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**STUDIES OF METABOLISM IN
CASES OF CHRONIC EMPYEMA OF
THE PLEURA WITH REFERENCE TO
AMYLOID DEGENERATION**

BY

O. PERÄSALO

HELSINKI 1948



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FROM THE SECOND SURGICAL UNIVERSITY CLINIC, HELSINKI,
AND THE DEPARTMENT OF MEDICAL CHEMISTRY, UNIVERSITY
OF HELSINKI. DIRECTORS: PROFESSOR P. E. A. NYLANDER, M. D.
AND PROFESSOR P. E. SIMOLA, M. D., PH. D.

STUDIES OF METABOLISM
IN CASES OF CHRONIC EMPYEMA OF
THE PLEURA WITH REFERENCE TO
AMYLOID DEGENERATION

INAUGURAL DISSERTATION

BY

O. PERÄSALO

TO BE PUBLICLY DISCUSSED,
BY PERMISSION OF THE MEDICAL FACULTY OF THE UNIVERSITY
OF HELSINKI, IN LECTURE ROOM 3 ON MAY 31, 1948,
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HELSINKI 1948
MERCATORIN KIRJAPAINO

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PREFACE

I wish to express my gratitude to my esteemed instructor, Professor P. E. A. NYLANDER, M. D., the Chief of the Second Surgical University Clinic, Helsinki. This work was undertaken at his suggestion, encouraged by his especial interest in the subject. Professor NYLANDER has directed my work with unfailing helpfulness and has given me unsparingly of his advice. Working under him, while in charge of the Chest Surgery Department at the Clinic, from the beginning of 1945 when my investigations began, I was allowed to perform examinations on patients who were under clinical treatment there.

To my esteemed instructor, Professor P. E. SIMOLA, M. D., the Chief of the University Department of Medical Chemistry, I acknowledge my great indebtedness. Even earlier I had the opportunity to become acquainted with the technique of scientific research under his expert direction. While working at the Department I profited by his experience and his generous advice. I was also allowed to carry out my chemical studies at the Department.

To Professor A. SAXÉN, M.D., I am indebted for his valuable help in my patho-anatomical studies of patients with amyloid degeneration.

I wish to acknowledge my gratitude to Dr. E. TIITINEN, University Lecturer, for valuable advice received during the work. I also to thank Dr. Ö. HELVE, University Lecturer, for the helpful advice which has especially furthered my studies of lipid metabolism, and Dr. E. PONTEVA, for the guidance I received in the section dealing with the sugar content of blood.

To Professor J. HELLSTRÖM, M.D., of the Karolinska Sjukhuset, Stockholm, who afforded me an opportunity for thorough study of electrolyte and fluid balance in surgical patients under

Clinical treatment at the hospital, I beg to express my respectful thanks.

My thanks are further due to Miss LEENA ALITALO, Department Nurse of the Chest Surgery Department, First Hospital for Disabled Soldiers, Helsinki, and the Laboratory Nurses Miss ESTER KALERVO and Miss TORBORG HEDBÄCK for kind co-operation. Finally, I owe grateful thanks to Lector AUNE TUOMIKOSKI, Mag. Phil., for translating this thesis into English.

Helsinki, September 1947.

INTRODUCTION

Changes in metabolism have been the object of especial interest, in the last decade, both in the study of internal diseases and in surgery. The electrolyte-fluid-protein metabolism shows in some diseases changes which are of specific importance from the diagnostic, prognostic and therapeutic points of view. Pathophysiology, formerly a purely theoretical subject, has after the publication of many new findings become an increasingly important auxiliary science in clinical work. American investigators have especially distinguished themselves in these clinical investigations, but Scandinavian surgical literature also contains valuable studies, among which those of BOHMANSSON (1943 and 1944) deserve mention.

Disturbances in the electrolyte and protein metabolism should be watched with especial care, for if allowed to develop they may become fatal. Even slight disturbances tend to cause an aggravation of the primary disease and to prolong the *pre- or post-operative period*, as may be the case, for instance, in surgical material. In the mildest stages of the disorder the complicative symptoms are mostly rather vague. Analyses of the blood or the plasma may in these instances be helpful in corroborating the diagnosis before the disturbance has reached an advanced stage. Systematical studies of fluid balance contribute to a more accurate diagnosis than before by establishing such conditions as *hypochloremia*, *dehydration*, *alkalosis* or *acidosis*, while the analyses, on the other hand, disclose to us the presence of *ionic deficiency or excess*.

In a number of acute infectious diseases various studies have been made of protein and electrolyte metabolism, and carbohydrate and vitamin metabolism. The literature, also, contains

records of investigations performed in chronic surgical diseases such as tuberculosis and tumoral cachexia, and chronic osteomyelitis. Metabolism in chronic diseases of the respiratory organs, especially pulmonary tuberculosis, has been the subject of several studies. Other chronic infectious diseases of the respiratory canals, on the other hand, have not received attention in this respect, as has been pointed out expressly by the well-known Americans M. & O. BODANSKY (1944). I have thus found only infrequent mention in the literature of investigations carried out in chronic cases of empyema of the pleura.

In contrast to those chronic infectious diseases which are common in time of peace, *only few studies of metabolism treating aspects mentioned above have been made in cases of war injury and following chronic suppuration*. It might be supposed that in these instances marked changes in protein and electrolyte metabolism are likely to occur, especially in view of the continuous suppuration persisting for months and even years, the general condition which has often been gravely impaired, and the damage caused by the severe chronic infection to the organism. In the literature at my disposal only WACHSMUTH's (1943) study of protein metabolism in severe cases of wound infection, so called wound cachexia, and CONRAD's (1944) investigations on vitamin C metabolism in 16 cases of chronic wound suppuration tackle the subject. Three of the patients had an empyema cavity. Numerous investigators, as recognized, lay stress on the importance of vitamin C for the organism, especially in infectious diseases. Investigations on carbohydrate metabolism have often disclosed a lowering of the carbohydrate tolerance in connection with infectious diseases.

In view of the facts stated in the foregoing I have performed investigations on protein and electrolyte metabolism, and blood sugar and vitamin C determinations in chronic, especially traumatic cases of empyema of the pleura. Simultaneously, I have in these cases kept a special lookout for the possible development of amyloid degeneration and undertaken, in established cases, additional investigations. These special investigations, however, owing to after-war conditions, have been hampered by the lack or scarcity of several necessary reagents.

II

MATERIAL AND OBJECT OF THE INVESTIGATION

My investigations were performed in cases of *chronic empyema of the pleura* under clinical treatment at the Department for Chest Surgery connected with the Second Surgical University Clinic. Both in war time and afterwards the care of patients with chest injuries in our land was concentrated at this Department. The majority of my patients were soldiers who after having been wounded had developed chronic pleurisy. Owing to war time conditions I could not start these investigations earlier, and the material thus includes only a part of the patients who were under treatment at this Department for chest injuries. When working there as a Department Surgeon I was able to observe the clinical condition of these patients from day to day.

When conditions became more normal, non-traumatic cases of empyema of the pleura were also admitted at the Clinic. A certain number of the chronic tuberculous cases of pleurisy appearing in my investigation have developed as complications of traumatic empyema cases.

My material thus consists of cases in which the patients are affected with severe chronic empyema. These patients exhibited, when admitted for clinical treatment at the Clinic, even after repeated thoracostomic operations, a purulent fistula, or suppurating conditions following various thoracoplastic operations. Thus the clinical condition of the patients varied considerably at the outset of the investigations. Among the most severe cases were those in which, to eliminate the spacious cavity, the removal by means of different operations in the lateral wall of the thorax

surrounding the whole cavity was necessary.¹ The base of the large wound produced in this manner is the more or less thickened suppurating pleura visceralis, or the free surface of the lung. Even bronchial fistulas occurred in some cases.

In patients with a high temperature even considerable changes in electrolyte metabolism, such as hypochloremia and acidosis, may sometimes occur. The patients examined by me were not generally feverish, with the exception of occasional febrile states of short duration caused by suppurating retention or following operations undergone. Persisting fever occurred in some cases in connection with different complications (pulmonary tuberculosis, pericarditis etc.).

As the general condition of the patients was often severely impaired on account of prolonged illness, the operation had to be of such a type as to reduce the strain on the patient to a minimum. Several operations were thus generally necessary to eliminate suppurating cavities. As, in addition, these suppurating wounds often heal rather slowly, some patients were under observation for months, others remained under treatment for the whole period the investigations lasted.

The investigation material comprises 59 cases of chronic cases of empyema of the pleura. Of these 44 were traumatic and 15 non-traumatic. Of the latter 6 were tuberculous, 7 metapneumonic, and in two cases the pleuritis was followed by chronic empyema. Four patients, in addition, developed tuberculosis as a complication of traumatic empyema. In one case with pulmonary tuberculosis chronic empyema developed after an operation performed (pneumolysis). Amyloid degeneration occurred in 7 cases in all. These will be discussed more in detail in Chapter IX.

The patients were comparatively young, the majority were wounded privates, under 40 years of age. The age of the oldest was 54 and that of the youngest 19 years, the average age being 29 years. The number of patients between 19 and 29 years of age was 33, that of patients between 30 and 39 years 19, and 7 were over 40 years of age or older. Only one patient's age exceeded 50 years. Two cases were 47 years of age, the rest were 43 years

¹ I refer to J. S. AALTO's work, Studies of cardiac disturbances in cases of healed traumatic chronic empyema of the pleura. — *Ann. Chir. Fenn.* 1947. Suppl. 2.

old or younger. The lowest age limit just given belonged to 4 of the patients. Only two of the cases were women.

The following examinations were made on the 59 patients who were under clinical treatment:

- the serum protein
- the serum chlorides
- the alkali reserve
- the vitamin C of the serum.

The cell-volume percentage (haematocrite), the haemoglobin and red cell count of every patient were obtained, in addition, the daily intake of fluid and the daily amount of urine were observed, and the urinary chlorides and specific weight of the latter were determined. The non-protein nitrogen was also determined in a number of the cases.

In patients with amyloid degeneration the tests mentioned were accompanied by determinations of the serum albumin and globulin, the total cholesterol of the plasma and Congo red tests. Determinations of the cholesterol ester and lipid phosphorus of the plasma were made, in addition. In cases when albumin was present in the urine, albumin fractions were carried out. These supplementary tests were made on six of the amyloid patients in the material. Corresponding tests were also performed in 9 cases of chronic empyema, in whom no amyloid had been ascertained.

The sugar tolerance test was made in 23 cases, four of whom were tuberculous. The alkali reserve of these patients was determined at the same time.

The blood tests were made on the patients on their admission to the hospital. In severe prolonged purulent conditions following an operation the examinations were first made monthly or more often, depending upon the clinical condition of the patient. As is well-known, the operation in itself may occasion considerable changes in the consistency of the blood. I therefore undertook regular examinations also after operation in order to be able to estimate, more closely, those variations in the blood consistency under examination which are directly due to the operation. After the operative measures examinations were performed every second or every third day, until the values became normal or returned to pre-operative figures. As it was necessary, owing to the character

of the disease, to undertake several successive operations on most of the patients, the blood changes were mostly observed regularly only after one operation, and at other times when the clinical condition of the patient permitted it. The protein and chlorides were examined regularly after the operation in 16 cases, the alkali reserve in 15 patients and the vitamin C in 15 cases.

In 13 chronic empyema cases the determinations were also made after recovery¹.

Using the cases as *comparative material*, I examined the protein, electrolyte and vitamin C metabolism of 30 patients who were under clinical treatment. 9 of them were cases of bronchiectasis, 9 had a pulmonary abscess, 3 were affected with pulmonary carcinoma, and 7 with acute suppurative pleuritis, 2 being patients suffering from pulmonary tuberculosis. Of the acute cases of suppurative pleuritis one was tuberculous and one, in addition, affected with lues cerebrospinalis. These cases from my comparative material appear in Table 6. The comparative material, in addition, contained 5 cases of amyloid degeneration, in one of whom the primary disease was chronic osteomyelitis, in one actinomycosis, in one tuberculous empyema and peritonitis, and in two bronchiectasis. The patients were subjected to examinations of the same character as those performed in the amyloid cases which developed in conjunction with the cases of chronic suppurating pleura.

Determinations of the protein and the chlorides of the serum, and the alkali reserve were made, in addition, in 10 normal cases, and corresponding studies were undertaken of physiological variations in 5 cases of indifferent diseases. The fasting rate of blood sugar was determined in 8 normal cases. The Vitamin C of serum was examined in 20 control cases in all, in 10 of them in the spring and in the others in the autumn.

The main questions to which I have endeavoured to find answers through the afore-mentioned investigations are the following:

1. *Are there any changes in the protein content of serum in cases of chronic, specifically traumatic suppurating empyema of the pleura?*
2. *Are there any demonstrable changes in the serum chloride level in these cases of pleural empyema?*

¹ *As the recording of the 59 case-reports of cases would occupy too much space, I have decided to refrain from publishing the casuistry. It is preserved, for possible reference, in the archives of the First War Injuries Hospital, Helsinki.*

3. *Are there eventually some alterations in the acid base balance in these cases?*

4. *Are changes in the sugar content of blood demonstrable in cases of chronic empyema of the pleura and are there possibly some symptoms present, in these instances, implying derangement of the carbohydrate metabolism?*

5. *What is the quality of the changes in the vitamin C content of serum in cases of chronic empyema of the pleura?*

6. *Can any especial tendency to amyloid degeneration be demonstrated in these cases and what is the diagnostic significance of the Congo red test for finding out this fact? What is the nature of the disorder observed in the protein and lipid metabolism of these patients?*

III

METHODS

TECHNIQUE OF BLOOD DRAWING

The technique of blood drawing is of especial importance when studies are made of changes in the blood in chronic suppurative conditions of the pleura. In a later connection I shall discuss more in detail the specific errors occasioned by a faulty technique. In this connection I only mention some of the most important general points.

Venous blood was employed in all the blood tests. The blood was withdrawn from the vena mediana cubitis in the morning before taking food, the patient lying in bed with the arm stretched horizontally. Circular stasis by means of a rubber band was not generally used. By pressing the vein for a while centrally with the tip of the finger the drawing of the blood was in most cases successful. If circular stasis was employed, it was of as short a duration as possible, applied only when the needle was introduced into the vein. To effect an easy outflow of the blood without stasis, as large needles as possible were used and the blood was made to run off direct into a 10 cc. centrifuge tube. Only the blood required for the determination of the alkali reserve, about 6—8 cc., was obtained by means of the Record syringe. While observing the technical points just mentioned, the following additional measures were undertaken: Blood from a vein at the bend of the elbow was run off into a 10 cc. Record syringe containing a few drops of heparin and ca. 2 cc. of paraffin. For a double determination 6—8 cc. of blood was drawn. The blood was then run by means of a needle into a 15 cc. centrifuge tube at the bottom of which was ca. 2 cc. of paraffin. By holding the tip of the needle under the paraffin layer the connection of the blood with air can be prevented and thus also the evaporation of CO_2 from the blood. After centrifugation the determinations were made in the course of the same day.

About 16—18 cc. of blood were always drawn off at a time, of which ca. 6—8 cc. of heparin plasma for the determination of the alkali reserve and ca. 10—12 cc. for determining the serum protein, the chlorides and the vitamin C. Directly after the samples had been obtained the investigations were carried out at the laboratory of the Hospital.

TABLE 1

No.	The Quantity of Serum Protein	
	The Biuret Method	The Micro-Kjeldahl Method
C1	5.6	5.8
C2	5.2	5.0
C3	7.0	7.2
C4	6.4	6.4
C5	4.4	4.3
C6	8.1	8.1
C7	6.0	5.8
C8	3.9	3.9
C9	5.2	5.4
C10	6.7	6.9
Average (10)	5.85 per cent	5.88 per cent

METHODS USED IN INVESTIGATION

In order to reduce the possibilities of error to a minimum, all the determinations were performed by the same two nurses who were especially qualified for laboratory work. As the investigations took place at the laboratory of the Hospital itself, I was able to superintend the tests and also to take part in them. The investigations on the amyloid patients, such as determinations of the plasma lipoids and partly those of the albumin fractions of serum and the fractions of the urine protein were carried out at the Medical Chemistry Department of the University of Helsinki.

The procedures employed in my investigation are the following:

BLOOD

Protein

The determination of the protein of the serum was made by means of LEHMANN'S (1944) modification of KINGSLEY'S (1939 and 1940) biuret method. The procedure is based on the fact that in the presence of protein the alkalic copper sulphate solution is dyed into a violet colour.

The error limit is ± 0.1 — 0.2 per cent when the serum is clear. The errors are caused especially by haemolysis, a turbid (lipemia) and icteric serum. The values are in these cases too high.

Table 1 presents comparative studies of the serum protein performed by me by means of the biuret reaction and the micro-chemical method based on KJELDAHL'S principle for nitrogen determination¹, with different pathological serums.

¹ The name micro-Kjeldahl will be used in the text later.

As appears from the Table, the greatest divergencies were ± 0.1 — 0.2 per cent. When the values exceed 8 per cent or are under 5 per cent the ratios remain unchanged. The difference of the averages in ten different pathological cases is 0.03 per cent. In three cases the values yielded by the two methods coincided. When the values were under 6 or above 8 per cent double determinations were made in my investigations. KINGSLEY (1939) obtained similar findings in comparative investigations undertaken by him. LAURENT and LAMBERG (1947) also arrived at similar results.

This colorimetric micro-method is especially suited for clinical investigation series. The procedure is relatively rapid, and the determination of the serum protein can be effected by this means in about 35 minutes. Only 0.1 cc. of serum, moreover, being required, a continuous observance of the serum protein is not too much of a strain on the patient even in severe cases.

In the examined cases the protein fractions of the serum were performed by means of the same method. Control tests were made contemporaneously also by the micro-Kjeldahl method. The differences in the amounts of albumin and globulin established by these methods are fully comparable with those obtained for the total proteins.

Owing to a lack of reagents and various other requisites it was not possible, in the first stages of the investigation, to determine the albumin and globulin from the plasma by means of KJELDAHL's method. The determinations in question — for the sake of consistency — were also later made from the serum by the aforementioned technique.

Chlorides

The serum chloride determinations were made by WHITEHORN'S (1921) method. The quantity of other chlorides in the serum is small, so that the chlorides can be expressed as a NaCl content without the risk of noteworthy errors.

As the examinations were made immediately after the withdrawing of the blood, no paraffin protection was used in the process. After the precipitation of the protein from the serum (according to FOLIN-WU) the determination took place by means of silver nitrate and rhodan potassium.

Alkali Reserve (the amount of bicarbonate in the plasma)

The determinations were made with VAN SLYKE'S (1927) manometric apparatus by VAN SLYKE'S and NEILL'S (1924) method. Double determinations were performed in every test.

Vitamin C

In my investigation the determination of the Vitamin C of the serum was performed by making use of the metaphosphoric acid precipitation and dichlorophenolindophenol titration employed at the University Depart-

ment of Medical Chemistry, Helsinki, following FARMER and ABT (1935) more or less closely. As sometimes rather marked divergencies occur in the vitamin C quantity when determined by the various methods, the method I applied will be presented in the following:

The preparation of the standard solution. 50 mg. of 2,6-dichlorophenol-indophenol, 10 cc. of KH_2PO_4 solution (9.079 g/1000 cc.) and 20 cc. of Na_2HPO_4 solution (11.876 g/1000 cc.) are mixed in a graduated flask, and distilled water is added to make the solution 100 cc. in volume. The solution is allowed to stand a while and is then filtrated with ordinary filter paper. This solution, which must be renewed weekly, is diluted at need with water in the ratio 5: 100.

The execution. 2 cc. of serum is placed into a centrifuge tube and diluted with an equal quantity of water. To precipitate the proteins 4 cc. of recently prepared 5 per cent metaphosphorus acid is added, after which the compound is centrifuged for about 10 minutes. 4 cc. of the clear liquid in the centrifuge tube is transferred into a low porcelain bowl or a decanter standing on white paper. The standard solution is transferred from a byrette by drops, until the red colour produced stays for at least half a minute. The quantity of the standard solution corresponds, practically speaking, with the amount of ascorb'ic acid present in one cc. of blood.

In the method used by me, which is especially suited to clinical series of examinations, the influence of other reducing agents in blood has thus been left out of account. According to some investigators their share, however, is slight, as is evident from the chapter dealing with the Vitamin C content of blood. On the other hand, a certain number of errors are unavoidable also in such procedures in which the elimination of reducing agents takes place with a mercury acetate solution and when sulphuretted hydrogen is used for reducing the dehydroascorbic acid. These procedures, in addition, are by far more difficult to apply in extensive serial examinations. Further, I was able to note that in the procedure I used 2 cc. of 2 1/2 per cent metaphosphoric acid decolorized ca. 0.16 cc. of the standard solution employed. But since in the tests a part of the metaphosphoric acid used is in the sediment formed, it is difficult to estimate with certainty how great the decolorizing effect is in each specific case. It is probable, in addition, that some part of the ascorbic acid present in blood is absorbed into the sediment. In view of these facts no reduction was made in my investigations. Owing to the mentioned possibilities of error the vitamin C content of blood cannot be determined with absolute exactitude by any titrimetric procedure. As clinical investigation methods they, nevertheless, fully serve the purpose.

Blood Sugar

The determinations were performed by HAGEDORN-JENSEN'S (1923) well-known method.

The Red Cell Volume Percentage (Haematocrite)

The determinations were made by means of VAN ALLEN's haematocrite as a double determination.

Non-Protein Nitrogen

In the determinations FOLIN's (1919) well-known method was applied.

Lipids of the Plasma

The cholesterol and lipid phosphorus of the plasma were determined according to BLOOR (1914) from an alcohol-ether extract (1 part ether and 3 parts alcohol). The determination of the cholesterol took place on the basis of LIEBERMANN-BURCHARDT's colour reaction.

The lipid phosphorus was determined from the same extract as the cholesterol. A certain quantity of extract was evaporated down to dryness and burned on a sand bath. The phosphorus thus formed was determined photometrically, using aminonaphtholsulphonic acid and ammonium molybdate in sulphuric acid according to FISKE and SUBBAROW (1925), and LOHMANN and JENDRASSIK (1926).

The value indicating phosphatide in the Tables was obtained by multiplying the quantity of total lipid phosphorus by 25 (the phosphatides contain on an average 4 per cent of phosphorus). Owing to the special conditions following the war there were regrettable shortages in the early stages of the work. The lipid examinations planned were thus not carried out in every case.

Congo Red Test

The Congo red tests were performed by the method presented by BENNHOLD (1923) in the following way:

In the morning before the patient had taken any food 5 cc. of blood was drawn from a vein at the bend of the elbow direct into a centrifuge tube, and 10 cc. of 1 per cent sterile Congo red solution was injected immediately by means of the same needle into the vein. 3 minutes after the injection 5 cc. of blood was drawn off and the same quantity an hour later. In drawing the blood one should not use too fine needles, in order that the blood can be made to run without stasis. During the test the patient should, moreover, take no food.

The blood specimens obtained were allowed to coagulate by themselves and were centrifuged, after which the clear serum was pipetted. The extinction of the serum drawn was determined by photometry colorimetrically both after 3 minutes and after an hour, using the S 50 filter and a 2.5 mm. cuvette. The control cuvette was in both cases filled with native serum. The amount of the colour substance still present in the blood after an hour = $\frac{E_2}{E_1} \times 100$, E_1 being the extinction of the serum compared with

native serum after 3 minutes and E_2 after one hour. This is a simple way of determining the quantity of the colour substance that has disappeared from the blood.

The figure expressing the amount of dye which disappears from the blood within one hour is called by BENNHOLD the Congo red index (C.R.I.).

The specimen should be drawn with especial care, for prolonged stasis and haemolysis tend to cause errors. Haemolysis, in particular, is apt to produce markedly increased Congo index values. With a view to this I performed all these tests personally.

To prevent coagulation in the specimen to be drawn after 3 minutes, small amounts of physiological sodium chloride were injected into the same vein. Before the drawing of the specimen the blood was allowed to run for a while, so that the serum obtained in the specimen should not be diluted with sodium chloride.

URINE

Chlorides

The determinations were performed by the well-known BANG-LARSSON method.

Albumin

The *micro-Kjeldahl* method was applied in the determination of albumin in cases of amyloid degeneration.

IV

THE SERUM PROTEIN

SERUM PROTEIN IN NORMAL CASES

There are numerous investigations in the literature on the normal values of the protein amount in serum. The method of determination, in these investigations, is of course of certain importance. Earlier findings should therefore be consulted with certain reservation. The most reliable technique for the determination of protein and the one most widely used is KJELDAHL's method. SALVESEN (1926) made determinations by this method in 32 normal cases. The lowest value obtained was 6.3 per cent, the highest 7.9 per cent, the average being 7.0 per cent. LEHMANN (1944) regards the values ranging from 6.5 per to 8 per cent, when obtained by the biuret method, as normal. BING, NAESER, RASCH and RØJEL (1946) record a variation of values from 5.6 to 8.2 per cent in 87 normal persons. They used the methods of HENRIQUES and KLAUSEN (1932). LANGE (1946) studied 115 normal cases, both men and women. According to KJELDAHL the mean value was 7.4 per cent, the lowest 6.3 per cent and the highest 8.8 per cent.

When considering the results of different investigators we may regard the values 6.0—8.0 per cent as normal, the average being 7.1 per cent (BEST and TAYLOR 1945; MILAM and DURHAM 1946).

In normal cases, I made determinations of the serum protein of 10 healthy individuals. The highest value was 7.3 per cent, the lowest being 6.6 per cent, and the average 7.0 per cent, so that the normal values I obtained agree with those recorded by LEHMANN et al. by means of the same technique. The results of the investigations are presented in Table 2.

Influence of Various Factors upon Protein Concentration

Stasis is not only of theoretical but also of great practical significance. In a haemodynamical sense its effect is comparable to that of increased venous pressure. KROGH (1922) has shown that in typical stasis the capilla-

TABLE 2

SERUM PROTEIN AND CHLORIDES (NaCl), ALKALI RESERVE AND VITAMIN C
CONTENT OF SERUM IN NORMAL CASES

No.	Protein %	Chlorides mg %	Alkali reserve vol. %	Vitamin C mg %
I	6.8	603	62.9	0.40
II	7.0	603	57.9	0.33
III	7.2	607	60.6	0.40
IV	6.6	610	57.9	0.45
V	7.2	594	62.3	0.48
VI	6.6	622	52.6	0.51
VII	7.3	572	61.4	0.57
VIII	7.3	618	56.0	0.39
IX	7.2	595	62.0	0.44
X	6.7	624	52.9	0.48
Average	7.0	605	58.7	0.45

ries have extended and permeability has increased. The concentration of the serum is thus partly due to the flow of the fluid into the tissue and partly to the transition of the fluid, owing to a congestion of CO_2 , from the serum into the red blood cells.

The concentration of the serum depends upon the efficacy of the stasis and its duration. PETERS, EISENMAN and BULGER (1925) found that a five minute stasis caused a rise in the protein percentage from 6.9 per cent to 9.3 per cent. VAHLQUIST (1941) has stated in his investigations that a short stasis of about half a minute's duration occasions no changes in the concentration of the blood. After $2\frac{1}{2}$ minutes, on the other hand, the increase in the protein percentage of the serum could be several per cents.

The citrate and oxalate plasmas yield erroneous, mostly too low values. Manual work may increase the concentration of the serum considerably (LANGE 1946).

In my investigations I noted that in a majority out of 10 examined cases there was a rise in the values of the protein amount of the serum after a circular stasis of about $1\frac{1}{2}$ —2 minutes. These findings are presented in Table 3.

Physiological Changes in Protein Content

BÖHME (1911) made investigations on the quantity of the serum protein in *different seasons*. He noted in one case values ranging from 7.2 to 7.7 per cent in the summer months and values between 7.0 and 8.2 per cent in

TABLE 3
EFFECT OF STASIS ON THE SERUM PROTEIN AND CHLORIDE (NaCl)
CONCENTRATION, AND ON THE ALKALI RESERVE

No.	Protein %	Chlorides mg %	Alkali reserve vol. %	Stasis
I	6.8	603	62.9	--
	7.1	608	59.9	+
II	7.0	603	57.9	--
	7.0	605	57.1	+
III	7.2	607	60.6	--
	7.3	599	57.1	+
IV	6.6	610	57.9	--
	6.8	617	57.8	+
V	7.2	594	62.3	--
	7.4	595	59.1	+
VI	6.6	622	52.6	--
	6.6	624	52.5	+
VII	7.3	572	61.4	--
	7.5	568	59.3	+
VIII	7.3	618	56.0	--
	7.5	620	54.9	+
IX	7.2	595	62.0	--
	7.3	596	61.2	+
X	6.7	624	52.9	--
	7.0	618	52.7	+

the winter months. He was yet unable to state whether his observations were in agreement with the general rule. Several other investigators have explained the variations in the quantity of serum as due to temperature. A cold environment leads to concentration of the blood and the serum, a warm environment to dilution (BARBOUR and HAMILTON 1925 et al.). LANGE (1946), however, in his investigations, could not observe any noteworthy changes. It is evident that in addition to temperature many other factors may contribute to the results, such as food, work, radiation of light and infections occurring in everyday life.

In the *daily* variation of serum protein WINDFELD (1933) et al. could detect only slight changes. Table 4 shows that my results are in agreement with this. The determinations were made in 5 indifferent sick-cases during 6 days, except in one case on 5 days.

TABLE 4

PHYSIOLOGICAL VARIATIONS OF THE SERUM PROTEIN AND CHLORIDES (NaCl),
AND OF THE ALKALI RESERVE

No.	Day	Protein %	Chlorides mg %	Alkali reserve vol. %
C _I	1	7.3	605	60
	2	7.2	595	58
	3	7.2	605	59
	4	7.1	605	60
	5	7.0	600	60
	6	7.1	602	57
C _{II}	1	7.1	624	55
	2	7.1	615	55
	3	7.0	610	58
	4	6.9	600	61
	5	7.1	608	61
	6	7.0	603	61
C _{III}	1	7.4	608	57
	2	7.3	603	56
	3	7.3	608	55
	4	7.3	620	54
	5	7.4	617	59
	6	7.3	618	58
C _{IV}	1	7.2	600	62
	2	7.0	600	57
	3	7.3	600	63
	4	7.0	600	62
	5	7.0	597	60
C _V	1	6.5	603	61
	2	6.6	602	68
	3	6.4	594	66
	4	6.6	594	64
	5	6.6	599	64
	6	6.4	597	66

SURVEY OF EARLIER INVESTIGATIONS ON CHANGES IN SERUM
PROTEIN IN INFECTIOUS DISEASES

A decrease of the serum protein concentration in *acute infectious diseases* was established as early as 1909 by SANDELOWSKY.

BERGER (1922) has made thorough investigations by the help of reliable methods. He explained the changes in the protein percentage of serum in acute infections as follows:

All infectious diseases are characterized by disturbances in the formation of protein. In the first stage of the disease the new formation decreases, the consumption of protein increases. This produces a decrease in concentration, called *hypoproteinemia*. It does not attain its minimum until some time later. Then the values begin to rise slowly, reach the normal and exceed it. This increase is an expression of intensified organic function, a post-infectious *hyperproteinemia*.

PETERS, EISENMAN and BULGER (1925) noted in 5 different infectious diseases normal or slightly elevated values. The lowest value occurred in a case of lobar pneumonia (6.6 per cent) and the highest (8.6 per cent) in a patient suffering from bronchopneumonia with co-existent meningitis.

SUNDERMAN, AUSTIN and CAMAC (1926) examined cases of lobar pneumonia and observed that the total protein amount of the serum had fallen slightly during the febrile period, but returned to a normal value after the crisis.

SCHOCH (1926) studied protein changes of the serum in 8 acute infectious cases, of whom 5 were instances of croupous pneumonia, one of tuberculous pneumonia, one case of acute polyarthritis and one a scarlatina case. All the pneumonia patients exhibited a fall in the total protein amount below 6 per cent, but after the patients recovered the value rose rapidly and exceeded 7 per cent. In the rest of the cases, also, the values as a rule fell, yet remaining within normal limits, but the differences were distinctly smaller. At the onset of the disease the globulins showed a slight fall, later their amount increased. The albumins, instead, first increased, then decreased and finally again rose. The lowest serum protein values occurred in the early stages of an acute infection. According to SCHOCH the decrease in the amount of albumin is dependent upon the severity of the infection and the counter-reaction of the organism.

WACHSMUTH (1943) noted that in a private who had had an abundant haemorrhage and a suppurating wound accompanied by temperature the protein amount of the plasma varied from 4.2 to 5.5 per cent during 3½ weeks after he had been wounded.

Among *chronic infectious diseases* pulmonary tuberculosis, especially, has been the subject of investigations. ALDER demonstrated, as early as 1919, an almost constant hyperproteinemia in patients affected with pulmonary tuberculosis. Only in severe cachectic conditions the values had fallen. He also claimed that the hyperproteinemia was due to an increase of the globulins which was dependent upon the activity of the disease.

LÜTHY (1927) determined the total proteins of the serum in 158 patients

affected with pulmonary tuberculosis. In all the patients with a good outlook the serum proteins ranged from 7.0 to 9.1 per cent. In one instance when the patient had serofibrinous pleurisy, the values were regularly under 7 per cent (the lowest being 6.6 per cent). The values for patients with a bad prognosis were lowest, also generally preceding death. LÜTHY, likewise, had noted an increase of the globulins in cases of hyperproteinemia. He found this fact a valuable aid in estimating the condition of the patient.

EICHELBERGER and McClySKEY (1927) made corresponding investigations in 109 patients with pulmonary tuberculosis. The total protein percentage was either normal or slightly increased. The serum proteins were in 55 cases above 8 per cent and in 3 cases above 10 per cent. The lowest value was 6.0 per cent and the highest 11.1 per cent, the average being 7.1 per cent. The increase in the total protein was due to an increase of the globulins, which explains the fall in the ratio albumin—globulin.

COLLER, DICK and MADDOCK (1936), who made investigations on fluid balance in a series of 21 surgical patients, noted in their one single chronic empyema case a 6 per cent amount of proteins.

RATZAN and THOMPSON (1945) studied the post-operative variations of the serum proteins in intrathoracic diseases. Of the 15 cases 5 were chronic empyemas, of which 2 metapneumonic and the rest tuberculous. In the former the pre-operative values for proteins were 7.0 and 7.7 per cent and in the latter cases 7.5, 5.0 and 6.8 per cent.

In various acute and chronic diseases of the liver several investigators have been able to ascertain hypoproteinemia, as e.g. MYERS and KEEFER (1935), FOLEY, KEETON, KENDRICK and DARLING (1937) in cirrhosis. In these instances the amount of albumin, especially, has decreased, so that the ratio of albumin and globulin, normally varying between 1.5 and 2.5, can be below 1. The occurrence of hypoproteinemia in diseases of the liver is due to disturbances in the hepatic function. It is not unlikely that the liver is the site of the protein formation in the organism.

BRÖCHNER-MORTENSEN (1938) established hypoproteinemia in chronic pemphigus, with co-existent oedema. The investigator attributed this to the exudation taking place through the skin.

It is evident from the investigations made that in acute febrile infectious diseases the serum proteins are normal or slightly decreased. Several infectious diseases accompanied by fever and destruction of tissue are characterized by variations in the ratio of albumin and globulin and mostly by a relative increase in globulin. This is most regularly the case in tuberculosis. In these instances the total serum protein has often increased, and hyperproteinemia is present. Along with an improvement of the outlook of the disease or towards its final stages the globulin level shows a fall as do the total protein values. According to the available literature, instead, no extensive studies have been made of the behaviour of serum proteins in cases of chronic empyema of the pleura. In the six non-traumatic cases of chronic empyema mentioned in the foregoing the limit values of proteins were 5.0 and 7.0 per cent. Even in these instances the value falling below 6 per cent occurred in a tuberculous case.

OWN STUDIES OF CHANGES IN SERUM PROTEIN IN CHRONIC
EMPYEMA OF THE PLEURA

To evaluate the variations in the protein amount of serum correctly it is of especial importance to observe, contemporaneously, the concentration of blood. This is indicated by the haemoglobin amount, the red cell count and the volume percentage of the red cells. Of these, the haematocrite value is the most objective and more responsive to changes than the haemoglobin amount and the red cells (CARR 1944). The normal volume percentage varies from 35 to 45, and the error does not exceed 1 vol. per cent (AALKJÆR 1943). To what extent the haematocrite values are influenced by possible variations in the size of the red cells, due to e.g. osmotic and chemical factors, in connection with changes in blood, remains still an open question. The records in the literature differ on this point (SJÖVALL 1936; FORSSELL 1939; BRENNAN 1940 et al.).

In some cases, owing to the nature of the disease, several operations which are in themselves of importance in occasioning changes, were made upon the patients. By observing the corresponding alterations after the operations one is able to estimate more accurately the share of the operations in the changes under observation which take place in the blood consistency.

The serum protein values in the 21 first cases are presented graphically in Fig. 1—5. Several among these cases were under treatment almost throughout the period when the investigations were being made. Each of the graphic representations is accompanied by a Table showing the haematocrite, haemoglobin and red cell values thus that every point in the Figure has a counterpart of values in the Table. The results of my investigations in the cases 22—59 appear in Table 5.

Considering the intense chronic infection, the continuous sup-puration and, in many instances, the severe clinical condition, one might theoretically expect in these cases a marked decline in the serum protein level. Yet hypoproteinemia is a rare condition in chronic empyema of the pleura and occurs only in cases with co-existent amyloidnephrosis, immediately after operations, and in especially severe post-operative suppurative conditions of long

SERUM PROTEIN IN CASES OF CHRONIC EMPYEMA OF THE PLEURA
(CASES 1—21; FIGURES 1—5)

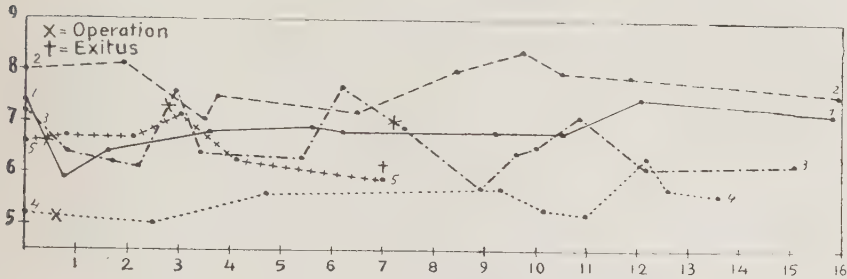


Fig. 1. — Cases 1—5. Ordinate: Serum protein concentration (g. per 100 cc.).
Abscissa: Time in months.

Table to Figure 1¹

Haematocrite Value, Haemoglobin and Red Cell Count in Cases 1—5.

No. 1	36	34	30	—	—	37	36	37	30	—
23/5. 45	—	62	56	54	58	63	69	63	63	71
	—	3.65	3.30	—	—	—	4.34	4.70	4.42	—
No. 2	34	—	36	—	35	37	42	43	39	—
18/6. 45	61	66	53	—	70	74	69	70	69	—
	3.44	3.90	3.33	—	—	4.20	4.15	3.87	4.50	—
No. 3	34	29	28	39	30	—	—	34	40	36
2/7. 45	69	59	63	79	64	—	—	67	70	71
	3.81	3.50	3.60	4.78	4.02	—	—	3.89	3.95	4.00
	46	39	—	—	—	—	—	—	—	—
	78	76	—	—	—	—	—	—	—	—
	4.34	4.32	—	—	—	—	—	—	—	—
No. 4	—	31	—	50	31	—	47	—	38	—
1/5. 45	—	67	—	90	83	—	87	—	—	—
	—	3.66	—	4.84	4.27	—	4.00	—	—	—
No. 5	30	24	25	24	32	30	—	—	—	—
4/7. 45	47	50	64	54	53	57	—	—	—	—
	3.64	3.12	3.53	—	—	3.55	—	—	—	—

¹ The haemoglobin has been expressed by the Sahli standard, which in Finland has been checked so that 100 per cent Sahli corresponds to an oxygen capacity of 18.5 vol. per cent of blood. The erythrocyte count is expressed in millions.

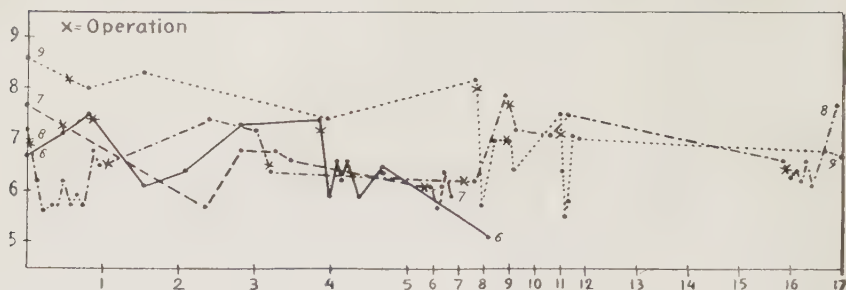


Fig. 2. — Cases 6—9. Ordinate: Serum protein concentration (g. per 100 cc.).
Abscissa: Time in months.

Table to Figure 2

Haematocrite Value, Haemoglobin and Red Cell Count in Cases 6—9.

No. 6	35	35	34	38	38	38	43	38	34	39	39
9/1. 46	63	65	60	67	64	76	78	71	70	66	66
	3.52	3.69	3.45	3.98	3.77	4.30	4.30	4.30	4.30	4.12	—
	30	35	43								
	69	74	80								
	—	—	4.84								
No. 7	47	43	39	43	41	42	39	46	42	40	41
1/2. 46	92	72	70	69	69	73	69	70	71	70	70
	5.07	4.40	4.21	4.34	4.54	—	—	—	—	4.54	4.69
No. 8	40	36	29	28	31	27	28	29	31	30	—
29/6. 45	77	72	67	64	62	63	65	65	64	62	—
	4.32	—	—	—	—	—	—	—	3.73	—	—
	30	29	31	35	30	36	34	30	34	41	37
	60	65	60	65	63	65	65	65	69	64	58
	3.65	3.59	3.45	3.93	—	4.10	4.30	4.16	4.14	3.99	3.62
	34	37	26	28							
	57	64	60	60							
	3.84	3.77	3.65	—							
No. 9	35	30	41	44	43	35	36	—	31	32	34
2/7. 45	67	65	74	80	68	62	59	74	57	80	74
	4.19	3.19	4.03	4.40	3.94	3.56	3.63	4.15	3.30	4.41	3.87
	28	31	32	24	39	36					
	64	66	70	69	90	85					
	3.50	3.63	4.20	4.38	4.93	4.58					

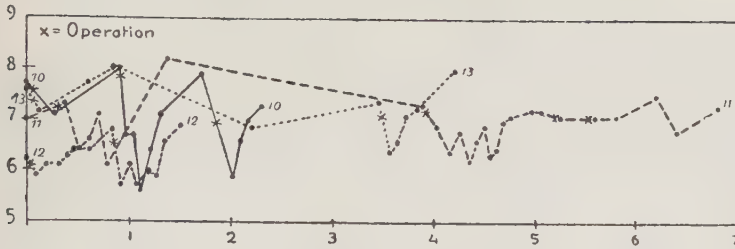


Fig. 3. — Cases 10—13. Ordinate: Serum protein concentration (g. per 100 cc.).
Abscissa: Time in months.

Table to Figure 3

Haematocrite Value, Haemoglobin and Red Cell Count in Cases 10—13.

No. 10	44	38	40	—	33	31	39	36	43	37	37
18/2.46	77	73	71	70	60	56	69	70	80	70	71
	4.33	4.06	4.35	4.00	3.15	3.06	—	—	—	4.00	3.90
	38	41									
	70	76									
	3.90	4.34									
No. 11	38	40	33	33	34	34	34	44	39	—	34
17/5.46	79	77	73	70	79	78	79	86	81	—	69
	4.37	4.40	3.91	3.70	4.02	—	4.00	4.58	4.43	—	3.80
	32	31	36	25	34	33	35	44	40	36	39
	64	61	62	57	58	63	70	78	72	68	58
	3.40	3.60	3.70	—	3.40	3.71	4.20	4.62	4.37	4.22	3.80
	27	31	38	32							
	68	68	68	60							
	4.22	3.76	3.75	3.32							
No. 12	39	31	35	36	39	38	38	43	35	33	29
13/4.46	72	57	62	65	66	65	70	71	63	58	55
	3.90	2.86	3.20	3.30	3.80	3.56	3.92	4.10	3.36	3.16	2.96
	30	29	32	28							
	55	58	57	62							
	3.01	3.23	3.41	3.54							
No. 13	42	36	38	33	39	—	38	35	35	36	41
3/12.45	68	64	65	72	64	—	63	58	64	64	72
	3.87	3.77	3.62	—	3.71	—	—	3.62	4.00	4.00	4.70

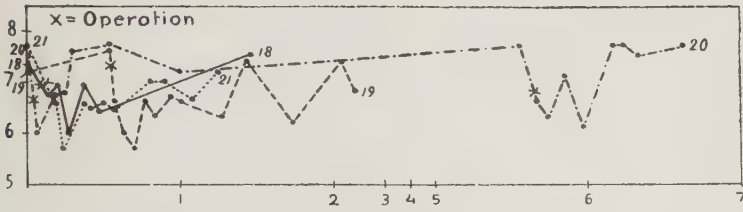


Fig. 5. — Cases 18—21. Ordinate: Serum protein concentration (g. per 100 cc.).
Abscissa: Time in months.

Table to Figure 5

Haematocrite Value, Haemoglobin and Red Cell Count in Cases 18—21.

No. 18	33	38	27	34	35	36	44				
12/3. 46	65	58	59	64	64	67	64				
	4.39	3.64	3.55	4.20	4.22	3.78	4.46				
No. 19	39	40	35	22	30	31	27	31	28	30	33
16/9. 46	83	78	67	71	59	60	55	62	56	58	62
	4.76	4.67	3.77	3.66	3.50	3.77	3.44	3.46	3.54	3.35	3.38
	22	32	33								
	60	60	65								
	3.25	3.71	3.77								
No. 20	32	28	22	27	31	30	—	45	42	39	38
14/5. 46	63	50	52	61	59	61	—	84	70	70	60
	3.78	3.31	3.64	3.52	3.87	3.95	—	4.86	4.50	4.52	3.44
	34	39	38	38	37						
	66	72	70	68	63						
	3.59	4.57	4.40	4.29	3.40						
No. 21	39	29	25	25	31	26	24	38	35	35	38
26/10. 46	70	64	56	48	54	54	62	70	68	72	70
	4.69	3.35	3.01	3.30	3.38	3.50	3.50	4.04	4.01	3.90	4.04

TABLE 5

SERUM PROTEIN AND CHLORIDES (NaCl), ALKALI RESERVE AND VITAMIN C CONTENT OF SERUM IN CHRONIC EMPYEMA OF THE PLEURA (CASES 22—59)

The Table also shows the haematocrite value (vol. %), the haemoglobin (Sahli), the red cell count (in millions) and the non-protein nitrogen of blood. The urine albumin was determined by Esbach's test and the urine chloride amount is expressed as a NaCl content (in grams).

No.	Date of test	Protein %	Chlorides mg %	Alkali reserve vol. %	Haemato- crite	Haemo- globin	Erythro- cytes	Vitamin C mg %	Non-protein nitrogen mg %	Urine		R e m a r k s
										Alb. ‰	NaCl	
22	31/8. 45	6.3	561		41	80	4,700	0.30	25	—		Chronic bronchial fistula.
	9/2. 46	6.7	584	54	40	90	5,100	0.26		—	24.9	
	12/6. 46	7.1	589	62	40	84	4,850	0.11		—	8.5	
	10/12. 46	6.9	595	63		80				—		
23	8/11. 45	6.3	553	67	41	93	4,890	0.42	30	—	12.6	Chronic bronchial fistula.
	31/1. 46	7.0	560	64				0.45		—		
	7/3. 46	6.9	602		44	95	5,090	0.27		—	12.1	
	12/4. 46	8.0	607	59				0.24		—		
24	23/5. 45	6.0	436	47	33	43	3,750	0.20	33	—	1.5	13/4 45. Thoracoplastia extra- pleuralis l. sin. 23/5 45. Revisio vulneris. 7/6 45. Exitus.
	28/5. 45	6.8	512	49	45	90	4,750	0.20	35	—	2.0	
	1/6. 45	8.0			38			0		—		
										—		
25	28/5. 45	7.0	503	47	28	56		0.39	30	—	6.1	22/5 45. Thoracocentesis l. sin. 3/8 45. Resectio costae et thoracostomia l. sin.
	8/6. 45	7.6	516	59	27	48				—		
	19/6. 45	6.8			27	49				—		
	4/7. 45	7.4	586	59	23	44	3,200	0.31	26	+	25.2	
26	10/7. 45	8.3	551	59	26	55		0.20	33	0.5		27/8 45. Exitus. 21/2 45. Thoracoplastia. 28/6 45. Exitus.
	19/6. 45	5.5	501	47	29	58	3,450			+		
27	29/5. 45	6.7	551		26	57	2,940	0.30	30	8		18/5 45. Thoracoplastia. 26/6 45. Thoracoplastia extra- pleuralis l. sin. 8/8 45. Exitus.
	13/6. 45	6.4	591	57				0.28		7	16.1	
	18/7. 45	4.1	478	36	34	65	3,420	0.23	26	15	1.8	
	7/8. 45	4.0	418					0.19		+		

28	26/6. 45 11/7. 45 7/8. 45 4/9. 45 14/9. 45 17/9. 45	6.5 6.6 6.0 5.7 4.4 5.0	559 605 511 423 446 495	57	36 28 28 34 49 45	76 66 61 75 49	4,300 3,800 3,550 4,170	0.34 0.34 0.36 0.29	24 27 28 40	10.7 7.8 6.8 3.7	26/6 45. Thoracoplastia. 25/7 45. Thoracoplastia extra- pleuralis l.dx. 23/9 45. Exitus.
29	9/4. 46 16/4. 46	6.2 6.7	559 562	49 55	36	68	3,730	0.28 0.32	33	10.5 7.7	9/10 45. Resectio costae et thoracostomia l.dx.
30	2/11. 45 17/11. 45 29/11. 45 7/1. 46 9/11. 46 ¹	7.0 6.6 6.5 8.7 6.6	573 538 541 539 618	62 57 59 55	44 33 45 46	69 72 75 76 87	3,750 4,070 4,070 4,440 4,800	0.39 0.49 0.55 0.58 0.30	28 30	19.4 9.2 28.3	16/11 45. Operatio plastica l.dx.
31	5/11. 45 13/11. 45 29/11. 45 29/12. 45 3/4. 46	7.7 7.5 6.9 7.2 7.3	553 525 576 578 597	59 60 59 61 54	39 42 38 30 38	80 80 75 73	4,420 4,490 4,420 4,380	0.34 0.30 0.49 0.87 0.39	30 33	10.4 11.2 21.7 21.3 21.4	12/11 45. Extractio corp. al. pulm. l.dx. Thoracoplastia.
32	3/5. 46 6/5. 46 8/5. 46 17/5. 46 12/11. 46 ¹	7.5 6.0 6.8 7.3 7.1	581 610 589 668 607	68 59 62 58 57	36 35 32 33 57	70 58 57 60 71	4,000 3,550 3,500 3,520 4,650	0.21 0.20 0.20 0.30 0.33	35	6.8 13.5 12.9 12.1 5.6	3/5 45. Thoracoplastia extra- pleuralis l.sin.
33	10/7. 45 13/7. 45 16/7. 45 18/7. 45 23/7. 45 25/7. 45 27/7. 45 13/11. 45 ¹	7.2 6.2 6.3 6.6 6.2 6.8 7.1	554 545 566 610 580 577 566	56	38 27 26 25 29 30 44	77 59 59 57 70	3,710	0.46 0.38	40	21.8	10/7 45. Thoracoplastia.
34	20/11. 45 26/11. 45 4/12. 45 28/12. 45	7.0 6.2 6.7 7.4	579 528 548 553	66 64 68 69	40 31 35 30	75 60 58 69	4,180 3,630 3,230	0.50 0.44 0.42 0.43	31 37 35	15.7 3.7 20.7 13.3	23/11 45. Thoracoplastia.

The date marked 1) refers to the examination when the disease had been cured.

TABLE 5 (Continued)

No.	Date of test	Protein %	Chlorides mg %	Alkali reserve vol. %	Haemato- crite	Haemo- globin	Erythro- cytes	Vitamin C mg %	Non-protein nitrogen mg %	Urine		R e m a r k s
										Alb. % ₀₀	NaCl	
35	10/4. 46	7.3	618	53	42	73	4,240	0.51		—	14.5	30/4 46. Thoracoplastia.
	2/5. 46	7.0	591	59	28	64	3,800	0.37		—	5.6	
	4/5. 46	7.0	514	63				0.30		—	4.6	
	7/5. 46	7.5	561	62				0.39		—	3.9	
	10/5. 46	7.1	576	67	23	62	4,400	0.36	31	—	10.1	
	14/5. 46	7.1	602	60	37	62	4,200	0.40	26	—	7.7	
	25/5. 46	7.5	558	65	31	61	4,000	0.37	32	—	18.3	
36	13/6. 46	7.8	589	61	29	68	4,200	0.38	44	—	10.9	8/5 45. Operatio plastica l.sin. 24/7 45. Operatio plastica l.sin. 17/4 45. Operatio plastica l.dx. 25/7 45. Operatio plastica l.dx.
	27/6. 45	8.2	597		37	75	4,420	0.28	37	—	1.7	
	24/7. 45	7.4	625	59	40		4,250	0.28	21	—	9.1	
	10/8. 45	6.3	536	28	28	63	4,000	0.29	31	—	11.4	
	11/11. 46 ¹	7.0	624	55	44		4,440	0.34		—	7.6	
	31/5. 45	7.2	594	52	45	78	4,380	1.00	54	—		
	25/7. 45	7.5	600	61	38	90	5,160	1.39	40	—	15.7	
37	11/8. 45	7.0	544	32	82	82	4,600	0.81	40	—	6.4	10/8 45. Thoracoplastia. 7/9 45. Thoracoplastia extra- pleuralis l.sin. 28/7 45. Thoracoplastia. 11/9 45. Thoracoplastia extra- pleuralis l.sin. 17/4 45. Operatio plastica l.dx. 25/6 45. Operatio plastica l.dx.
	11/9. 45	7.0	543	55	28	80	4,820	0.83		—	11.5	
	3/12. 45	7.1	564	58	44	83	4,870	0.83		—		
	9/12. 46 ¹	7.3	603	58	45	90	4,790	0.21		—	10.1	
	10/8. 45	7.0	545	58				0.32		—		
	14/8. 45	6.0	541		34	75	3,810	0.30	31	—	4.5	
	22/8. 45	6.2	569		42	64	3,610	0.24	31	—	7.1	
38	18/9. 45	6.4	602	60	28	62	3,520	0.41		—	12.5	28/7 45. Thoracoplastia. 11/9 45. Thoracoplastia extra- pleuralis l.sin. 17/4 45. Operatio plastica l.dx. 25/6 45. Operatio plastica l.dx.
	1/10. 45	7.0	545	63	31	66	3,620	0.48		—	17.5	
	7/6. 46 ¹	7.1	597	61	37		4,430	0.18		—		
	24/7. 45	6.7	605	57	36	75	4,200	0.27		—	4.8	
	30/7. 45	6.8	553	45	45	78	4,480	0.32	33	—	5.1	
	16/8. 45	6.4	528	34	72	72	3,700	0.29		—	6.5	
	17/9. 45	6.4	571	67	30	67	3,700	0.33		—	10.8	
39	5/4. 45	7.1	597	55	40	80	4,400	0.32	31	—	21.1	17/4 45. Operatio plastica l.dx. 25/6 45. Operatio plastica l.dx.
	25/6. 45	6.0	618	63	36	78	4,380	0.21	42	—	14.8	
	16/7. 45	6.2	536	57	35	70	4,100	1.26	36	—	7.4	
	2/11. 45	7.3	599	59	40	87	4,490	0.48		—	19.6	
	19/6. 46 ¹	7.3	608	56	37	80	4,520	0.36		—	6.5	
										—		
										—		

41	31/5. 45 24/7. 45 9/12. 46	6.8 7.9 7.7	572 672 622	43 58 57	84 85 82	4.950 4.460 4.490	1.10 1.44 0.19	40 30	— — —	2.8 10.0	9/5 45. Operatio plastica l.sin.
42	22/9. 45 22/9. 45 ¹	7.0 7.5	532 591	63 63	82 81	4.300	0.26 0.43	25	— —	9.9	2/6 45. Thoracoplastia.
43	11/7. 45 24/8. 45 29/8. 45 22/9. 45 19/6. 46 ¹	7.5 6.4 6.3 7.2 7.1	591 531 521 562 603	65 36 38 33 63	75 80 72	4.130 4.350	0.29 0.20	30 27	— — — — —	12.5	4/5 45. Thoracoplastia extra- pleuralis l.dx. 21/8 45. Thoracoplastia extra- pleuralis l.dx.
44	23/7. 45 1/12. 45 7/12. 45 28/12. 45 6/6. 46 ¹	6.9 6.5 6.9 6.7 6.9	546 548 515 553 561	53 59 66 62 63	78	4.480	0.75 0.27	—	— — — — —	16.9	3/5 45. Thoracoplastia et myo- plastia l.dx. 5/12 45. Incisio.
45	2/7. 45 16/8. 45 17/9. 45 21/9. 45 5/10. 45 2/4. 46	6.2 7.2 8.2 6.8 6.8 6.2	544 557 544 587 574 592	62 61 61 62 62 62	73 69 74 63 60 78	4.880 4.700 4.040 4.880 4.220 3.950 3.390 4.380	0.34 0.31 0.41 0.76 0.21	31 38	— — — — — — — —	11.5 3.2 5.4 2.2 8.7 9.9	14/6 45. Thoracoplastia extra- pleuralis l.sin. 18/7 45. Incisio. 17/9 45. Thoracoplastia.
46	26/7. 45 18/8. 45	6.8 7.4	552 610	61 39	65	3.780 4.360	0.43 0.37	35 40	— —	10.1 10.6	15/6 45. Thoracoplastia.
47	12/6. 45 26/6. 45 25/10. 45 ¹	6.6 7.7 7.7	558 566 617	50 58	80 79 75	—	0.21 0.62 0.61	— 26 35	— — —	12.9 12.6 10.3	7/7 45. Thoracoplastia extra- pleuralis l.sin. 13/6 45. Thoracoplastia extra- pleuralis l.sin.
48	10/6. 45 19/7. 45 31/7. 45 16/8. 45 21/9. 45 21/6. 46 ¹	7.2 7.6 6.2 6.8 7.5 6.8	584 589 457 528 536 602	43 42 34 34 55 64	90 83 77 73 53 85	4.790 4.400 4.160 3.240 4.500	0.22 0.24	37 37 35 37	— — — — — —	12.1 7.5 4.1 7.2 5.8 14.9	26/7 45. Thoracoplastia. 14/9 45. Thoracoplastia extra- pleuralis l.dx.
49	5/9. 45 13/9. 45 19/9. 45 1/10. 45	7.4 5.9 7.0 6.5	508 545 585 602	58 55 54 68	82 68 61 72	4.650 3.760 3.420 3.990	0.25 0.39 0.37 0.41 0.39	37 40 31	— — — —	7.7 1.1 6.3 14.9	8/9 45. Thoracoplastia.

The date marked 1) refers to the examination when the disease had been cured.

TABLE 5 (Continued)

No.	Date of test	Protein %	Chlorides mg %	Alkali reserve vol. %	Haemato- crite	Haemo- globin	Erythro- cytes	Vitamin C mg %	Non-protein nitrogen mg %	Urine		R e m a r k s
										Alb. % /100	NaCl	
50	4/9. 45	6.6	545	58		86		0.30				10/9 45. Thoracoplastia.
	11/9. 45	6.7	482	63	40	76	4120	0.24	37		16.6	
	13/9. 45	6.0	566	63	30	65	3580	0.41			5.2	
	19/9. 45	6.3	573	65	33	68	3740	0.35	30		11.5	
51	20/6. 46 ¹	6.2	595	60				0.25				4/10 45. Thoracoplastia extra- pleuralis l.sin.
	2/10. 45	6.7	579	64	42	90	5020	0.72	30		13.8	
	8/10. 45	5.8	568	65	36	62	3600	0.67	28		7.4	
	22/11. 45	7.8	578	62	42	87	4800	0.68				
52	31/1. 46	7.9	575	56	42	81	4520	0.38			18.4	19/1 46. Thoracoplastia extra- pleuralis l.sin.
	8/6. 46	7.3	591	59	41	91	5610	0.41			7.3	
	8/11. 46	7.5	607	56	52	88	5180	0.30				
	22/9. 45	7.0	543	60	37	75	4070	0.35	31			
53	24/5. 46	7.1	584	56	39	75	4230	0.33	30		9.1	Chronic bronchial fistula. 24/4 45. Thoracoplastia.
54	14/6. 45	6.6	594	68	32	63	4020	0.27	30		16.3	
	18/7. 45	6.4	561	54	32	75	4630	0.32	24		5.6	
	23/8. 45	6.3	537	58	45	78	4620	0.28	31		7.9	
55	30/5. 45	7.8	536	52	33	70	3980	1.10	24		3.5	26/3 45. Thoracoplastia extra- pleuralis l.dx.
	19/7. 45	7.7	571	63	37	66	3940	0.38	33		3.6	
	23/8. 45	6.5	528		37	72	3950	0.19	35		4.3	
56	13/2. 46	7.9	569	56	50	90	4850	0.36	27		11.3	27/4 45. Thoracoplastia.
57	23/12. 46	7.1	610	58	32	70	4100	0.25			8.0	
58	18/4. 46	7.1	615	54	51	87	5100	0.27			10.2	
59	3/7. 45	6.9	594	55	43	83	4780	0.37	31		27.3	

The date marked 1) refers to the examination when the disease had been cured.

duration. In 59 cases the lowest value, *directly independent of operations*, was 5.0 per cent (Case 4) and the highest 8.7 per cent (Case 30). By classifying the results obtained into groups one gets a clearer notion of the protein amounts present. As in many instances the investigations were performed during a relatively long period, *the first value which is completely independent of an operation* was in every case taken into account. In cases which at the outset of the investigations were under treatment at the Hospital, at least 5 weeks had then elapsed from the operation. Hypoproteinemia, with values falling below 6 per cent, was then present only in the cases 4, 5 and 26. These were, however, complicated by amyloidnephrosis, with accompanying severe albuminuria, which evidently serves as a primary explanation for the hypoproteinemia. In Case 5 hypoproteinemia did not occur until the urine had started to excrete albumin. 7 cases yielded low but yet normal values, with the serum protein ranging from 6.0 to 6.4 per cent. In 21 cases the values were between 6.5 and 7.0 per cent and in 28 cases 7.1 per cent or over. Thus in 31 cases out of 59 the serum proteins were below the average normal value (7.1 per cent). The size of the pleural cavity had no demonstrable influence upon the protein amount of the serum. In 10 cases with a total cavity and no preceding operations excepting thoracostomy, the minimum values were 6.2 and 6.5 per cent (Cases 29 and 28) and the highest 7.6 per cent and 7.9 per cent (Cases 13 and 56). Among these cases No. 29 presented a low fever and an abundant secretion of pus from the pleural cavity. Case 56 was a tuberculous empyema with an established elevated haematocrite value, which points to possible dehydration.

Figures 2—5 show the serum proteins also *after operations* which were carried out in Cases 6, 8—16 and 18—21, and Table 5 those in Cases 32 and 33. The fall in the serum proteins after operations in these 16 cases was on an average 1.3 per cent, varying from 0.3 to 2.0 per cent. The Cases (9, 10 and 21) with abundant haemorrhage at operation, showed the greatest fall in the serum protein level. The lowest value occurred as a rule on the 2nd—6th day following operation. In two cases (8 and 11) the minimum protein value was met on the 10th day. The former of these had a severe infection and the latter exhibited an ample secretion of pus after thoracostomy. The cell volume percentage, the haemoglobin and the

red cell count usually fell at the same time. By means of transfusions of whole blood and plasma it was, however, possible to raise the reduced protein amount of the serum. Following such factors as general condition, operation, the degree of haemorrhage and wound infection and transfusions of whole blood and plasma, the pre-operative normal value of serum proteins re-established itself in 14 cases in a period varying from 1 to 5 weeks. In two cases the otherwise normal values did not return to the pre-operative figure during treatment at the Hospital.

THORNTON, ADAMS and SCHAFER (1944) stated that in consequence of major chest operations the plasma proteins decreased by 1.0 per cent on an average. The change was constant in 31 out of 32 cases and took place on the 3rd—5th post-operative day. The haematocrite value, the haemoglobin percentage and the red cell count fell, likewise. Yet only two of the operations were thircoplatic measures in an empyema following pneumonectomy. RATZAN and THOMSON (1945) found that out of 15 cases in whom various operations had been undertaken for pulmonary or pleural diseases, the serum proteins were restored in 11 to normal pre-operative values in the course of 2 months.

In severe prolonged suppurative conditions following operations, the patient's general condition being impaired, severe hypoproteinemia was sometimes present. In Cases 27 and 28, which terminated fatally, the lowest serum protein values, in my investigation, were 4.0 and 4.4 per cent about 6 and 7 weeks after performed operations. In the former of these amyloidosis was a co-existent condition, and the urine contained a large amount of albumin. Case 26 resembled this case in character; the serum protein value was 5.5 per cent. Yet, in Case 27, hypoproteinemia did not manifest itself until during the severe wound infection, when, in addition, oedema was noted. This was probably due to hypoproteinemia caused by a serious kidney affection. In the rest of the cases no swelling was observed. In Case 5 the amount of serum proteins was 2 days before death 5.9 per cent, and albuminuria was present. In five earlier examinations, when there was no albumin in the urine, the values ranged from 6.3 to 6.9 per cent. Case 24 was a parallel instance which, however, yielded normal values before death, evidently owing to dehydration. This patient had no albumin in the urine. All these cases, which led to a fatal end, were subjected to operations on account of a total empyema cavity, and the wound suppurated

profusely. In Case 5 only thoracostomy was undertaken. In the febrile Case 25, with a small empyema cavity, the amount of serum protein was 8.3 per cent about 6 weeks before death, and the values yielded by the other examinations were likewise normal.

In other prolonged suppurative conditions, also, lowered total protein values of the serum could be noted. Thus in Case 1, as long as 5 weeks after operation, the serum proteins were 5.9 per cent, and in Cases 3 and 7 correspondingly after about 6 and 7 weeks 5.7 per cent. In the first case the whole lateral wall of the empyema cavity was removed, and the suppuration was relatively abundant. The pus formation continuing in comparative abundance for about 10 months, the protein amount of the serum varied from 6.4 to 6.9 per cent. After about 16 months, when the wound surface had epithelialized almost completely, the protein concentration was 7.2 per cent. Another case of the same character is No. 3 in which, after persevering suppuration low but still normal values were obtained, such as 6.1 and 6.2 per cent. In Case 7 an empyema cavity was likewise opened, but it was smaller than in the just mentioned cases, and the protein amount varied in the course of several months between 6.4 and 6.8 per cent. Evidently due to repeated operations, the values did not reach the pre-operative level. The cases 2, 6, 8, 9, 10, 11, 36, 37, 41 and 55 were similar instances. In spite of prolonged suppuration a low normal value (6.1 per cent) was noted only in Case 6. Case 2, which was tuberculous, yielded values which were on the upper limit to the normal, and can even be interpreted as pointing to mild hyperproteinemia (8.4 per cent). Along with an impairment of the general condition, in this case, the serum proteins also showed a fall (7.0 per cent), and increased again when the general condition improved. In Case 55, also, which was tuberculous, the serum proteins showed a decrease together with a deterioration of the general condition (from 7.8 per cent to 6.5 per cent).

Evident mild *dehydration* was present in 7 cases (4, 7, 9, 24, 51, 56 and 58). In these cases there was a suppurating fistula leading into the pleural cavity or the cavity had been opened. In Case 4, in the fourth examination, the haematocrite reading was 50 per cent, and both the haemoglobin (90) and the red cell count (4.84 mill.) showed a rise in comparison with other examinations made in the same patient. In Case 7, in the first examination, the haemato-

crite value was 47 vol. per cent, the haemoglobin 92 and the red cell count above 5 millions. In Case 51, in the last examination, the haematocrite reading was 52, the haemoglobin 88, and the red cell count over 5 millions. In Cases 56 and 58 the cell volume percentage was 50 and 51, the haemoglobin 90 and 87 and the red cell count 4.8 and 5.1 millions. In Case 9 and 24, on the other hand, the haematocrite value was, evidently owing to anaemia, normal (35 and 45 vol. per cent). The haemoglobin of the former was 67 and the red cell count 4.1 millions. The corresponding values were in the latter case 90 and 4.7 millions in spite of the very poor clinical condition. Only in Case 9 the urine amount was slightly reduced (600 ml.) and the specific weight of urine (1033) was somewhat higher. Evident mild hyperproteinemia, due to dehydration, was present only in Case 9, in which the protein amount of serum was in the examination in question 8.6 per cent.

In cases of *chronic bronchial fistula* (Nos. 22, 23 and 54) the protein values were low but yet normal (6.3 per cent). In Case 22, with the fistulas closing, the serum proteins were on the increase, as they were in Case 23 when there was an improvement in the general condition.

In 10 cases of *tuberculous chronic empyema* (Nos. 2, 4, 18, 19, 52, 53, 54, 55, 56 and 57) the serum proteins varied between 5.0 and 8.4 per cent. In Case 2 the protein level even seemed to point to mild hyperproteinemia. In Cases 2 and 55 along with an impairment of the general condition, the amount of serum proteins decreased, as in Case 54, where there was a co-existent chronic bronchial fistula.

It is interesting to note that *in several cases after operation, during the patient's convalescence, when the general condition, owing to the healing of the wound, was good, and when the wound surface was granulating, the values obtained were higher in proportion than in the other examinations, while at the same time there was no dehydration.* The protein concentration was then often higher than when the empyema cavity was fully eliminated and the patients had recovered. In some cases there were even some indications of mild hyperproteinemia (Nos. 9, 10, 17, 30, 36, 41 and 45). Thus in Case 30 the serum protein concentration was 8.7 per cent. This is possibly a consequence of the increased activity of the organs producing protein. The

chronic infection occasions derangement in the formation of protein substances, which leads to a reduction of the protein reserve. However, with the extensive wound surface granulating and healing, the need of the organism for substances containing protein has increased. Not improbably this fact stimulates the organs producing protein to an intensified activity, which gives rise to »hyperproteinemia.» BERGER (1922) mentions, when discussing acute infections, so-called »postinfectious hyperproteinemia.» Of chronic infections, on the other hand, I have been unable to find any corresponding studies in the literature. The regenerative capacity of the proteins in the organism seems to be considerable, as was shown by WHIPPLE (1938), for instance, in his experimental investigations. Patients who are under clinical treatment also not infrequently present normal protein values in spite of a great loss of albumin (nephrosis, ascites, haemorrhages).

As it has become evident from the foregoing, low values of serum protein occurred in some cases of chronic empyema of the pleura. In severe prolonged suppurative conditions after operations evident hypoproteinemia was observed in some individuals. A slight tendency to hyperproteinemia is present in one tuberculous patient.

Comparative Material (Table 6)

No marked differences could be noted in the serum protein concentration of chronic suppurating empyema cases in comparison with various chronic diseases of the lungs and acute pleural suppurative inflammations. The limit values, which were 8.7 per cent and 4.0 per cent in the investigation material, were in the comparative material respectively 8.4 per cent (Case 81) and 5.0 per cent (Cases 70 and 82). While before operation no hypoproteinemia was present in cases of chronic pleural empyema, values falling below 6.0 per cent were observed in 6 out of the 30 cases in the comparative material, without any operation more serious than thoracostomy having been performed in these cases before the examinations. In 9 cases of bronchiectasia and 3 cases of carcinoma of the lung the values were normal. In 3 cases of pulmonary abscess out of 9, on the other hand, the values fell below 6 per cent, and likewise in one of two cases of pulmonary tuberculosis and in two out of 7 suppurative acute cases of pleuritis. These hypoproteinemia cases either exhibited a rise in temperature or the general condition was very poor, the lowest values occurring in severe cachectic conditions which resulted in death.

Discussion of Results

According to VARCO (1946) the most important reasons for hypoproteinemia are the following: 1) Increased rate of metabolism. 2) Augmented rate of protein loss. 3) Decreased protein intake. 4) Reduced capacity of fabrication of protein.

When estimating the reason for the reduction of the serum protein concentration in such cases of pleural empyema where this phenomenon was observed, all the four factors just mentioned must be taken into account. When the fall in the protein percentage is due to an *increased rate of metabolism*, then the combustion of body protein takes place more rapidly than normal. The process of supplementation then occurs at the expense of protein stores, if the protein content of the food consumed has not increased sufficiently. In febrile infectious diseases there is often a simultaneous loss of appetite, which contributes, secondarily, to a reduction of the protein substance in the organism. In my own investigations the values are variable as far as the febrile cases are concerned. Thus two (Nos. 10 and 25) showed even relatively high normal values. In the rest of the cases (Nos. 5, 12, 29 and 55), instead, the amount of albumin varied from 6.2 to 6.9 per cent while there was fever. In Case 5 hypoproteinemia did not manifest itself until the condition had been complicated by amyloidnephrosis, in spite of the persisting fever. In this case, it is true, transfusions of plasma and whole blood were administered to the patient. In case 29, with a continuous abundant discharge from the spacious pleuritic cavity, the protein amount of serum rose when the fever vanished. In Case 55 the proteins showed a marked fall when the patient was in a febrile state.

The reduction of the serum proteins on account of an *increased rate of protein loss* is the first factor to be considered when the hypoproteinemia which is present in cases of chronic pleural empyema is to be accounted for. The purulent discharge from a suppurating pleuritic cavity may amount to several hundred cubic centimeters of fluid daily, with a protein concentration of 4 to 21 per cent (MAUBIAC 1936; RATZAN and THOMPSON 1945). WACHSMUTH (1943) found in 8 patients who had been wounded in the lung, in the course of 10 days on an average, before the introduc-

tion of the Bülau drain, 51 grams of protein in 802 ml. of discharge, and after the drain had been applied 126 grams of protein in 1960 ml. In one case, in which the loss of protein was greatest, the quantity of protein in an amount secreted during 10 days (4150 ml.) was 263 grams. Since the discharge consists mainly of plasma, it is evident that in cases like this the need for proteins in the organism has grown considerably. With concomitant fever the metabolism is increased and the consumption of protein has grown. If the protein amount consumed is not adequately compensated with food rich in proteins, by transfusions of whole blood or plasma, hypoproteinemia will follow. Also after operation, when the wound is healing, loss of protein takes place through the granulating wound surfaces as a consequence of both exudation of the plasma and suppuration. The special significance of protein substances for the healing of the wound is, in fact, emphasized by several investigators (AREY 1936; THOMPSON, RAVDIN and FRANK 1938 et al.). It is evident that cases in which albumin, in addition, is secreted by the urine, manifest the greatest loss of protein.

Furthermore, the *bacteriotoxic influence of wound infection* occasions *injury to the walls of the blood vessels*, as has been noted by SCHALLOCK (1943). This bacterial intoxication is enhanced by the toxic products of protein disintegration (amides) taking place in necrotic portions of the tissue. The substances in question have the quality of dilating the blood vessels. Due to these detrimental factors the permeability of the blood vessels has increased, which results, when plasma passes into the tissue from the blood vessels, in oedema. This occasions a fall in the protein level of the blood.

It is difficult to estimate to what extent the hypoproteinemia present in each of my cases is due to the formation of pus or to the intoxication caused by the infection. In severe cases leading to death *inanutition* and consequent disturbance of protein *resorption* are evidently of some importance.

In consequence of the severe *infection* present in cases of chronic pleuritis and prolonged suppuration the bacterial toxins act as an additional factor in impairing *the function of various organs*, causing *a decline in the general condition* and often also *loss of appetite*. In the last-mentioned instance when there is not uncommonly an increased need for protein, the organism must continuously take recourse to its protein reserve. If there is no corresponding rise

in the dietary intake of protein, the serum protein declines. In my cases of chronic empyema of the pleura the diet has been inadequate, for several of the patients have had no desire to eat. While hypoproteinemia has resulted only rarely, except immediately after operation and in severe wound infections of a long duration, the patients have clearly been obliged to make use of their protein supply. There is good evidence to support the view that in patients with this chronic disease the serum protein reserve has been deficient. In spite of vigorous treatment it has proved impossible, in some severe cases of hypoproteinemia, to produce any rise in the serum protein level. This may possibly be due to the reduced capacity of the *protein fabrication*, which is at present supposed to take place in the liver. It has also been suggested that the serum proteins are formed in the tissue cells which under certain conditions transmit their so-called labile protein into the serum. However, the mechanism of the origin of serum protein has not yet been fully elucidated (WUNDERLY 1947).

Summary

In cases of chronic empyema of the pleura without amyloid nephrosis the serum protein concentration was normal before operations carried out, though in a few cases low values, yet falling within normal limits, occurred. The extent of the empyema cavity had no bearing on the quantity of the serum proteins. After operation the serum proteins decreased in 16 examined cases on an average 1.3 per cent in the course of 2—6 days. At the same time the haematocrite, haemoglobin and red cell values fell, likewise. After operation the values were restored to a normal pre-operative level in from one to five weeks, depending mainly upon the operation, the amount of haemorrhage and the intensity of the infection.

Hypoproteinemia (below 6 per cent) occurred, except directly after operation, only in some severe post-operative suppurative conditions as late as after 5—7 weeks. The lowest values (4.0 and 4.4 per cent) were noted in two cases in the terminal stage of the disease. Only one of these patients had albumin in the urine. In the four cases of amyloidnephrosis hypoproteinemia was present. In several cases the accompanying fever seemed to bring about a reduction in the protein content of serum.

After operation, while the empyema cavity was closing and the general condition of the patient showed improvement, so-called »post-infectious« hyperproteinemia could be noted in some cases. Elevated protein values, in comparison with other examinations, occurred in these instances, even to the extent of implying a tendency to mild hyperproteinemia. In severe prolonged suppurative conditions dehydration was sometimes present.

The decrease in serum proteins when it occurs, is in my opinion mainly due to the loss of protein in the secretion from the wound and, besides, the intoxication caused by the severe chronic infection and the consequent increased decomposition of protein and damage to the blood vessels. Inanition, furthermore, is of some importance in this connection, also the possible reduced capacity of protein fabrication and the continuous decline in the protein reserve.

V

THE SERUM CHLORIDES¹

SERUM CHLORIDES IN NORMAL CASES

The NaCl content of serum varies relatively little in normal individuals. According to various investigators the limit values are 560 and 630 mg. per 100 cc. In BRIGGS's (1923), and MÜLLER's and QUINKE's (1927) investigations the lowest limit is 560 mg. per 100 cc. PETERS and van SLYKE (1937) regard 577 mg. per cent and 630 mg. per cent as limit values. M. and O. BODANSKY (1944) record as an average normal level 596—620 mg. per 100 cc., and according to HAWK, OSER and SUMMERSON (1947) the NaCl content of serum is normally from 570 to 620 mg. per 100 cc.

Table 2 represents the NaCl values of serum determined by me in ten healthy individuals. The lowest value was 572 mg. per 100 cc. and the highest 624 mg. per 100 cc., the average being 605 mg. per 100 cc. The values I obtained were thus in agreement with the normal values just mentioned. A serum chlorine content under 340 mg. per 100 cc. (corresponding to below 560 mg. of NaCl per 100 cc.) may be regarded as a sure sign of hypochloremia (LAUTROP and MADSEN 1942).

Influence of Various Factors upon Chloride Concentration

As a result of *venous stasis* fluid and salts are conveyed from the blood serum into the tissue, and a consequent reduction of chloride concentration takes place (DAUTREBONDE, DAVIES and MEAKINS 1923, PETERS, BULGER, EISENMAN and LEE 1926, et al.) The outflow of chlorides from the serum is then proportionally larger than that of fluid. The fall in the ratio $\text{Cl}:\text{H}_2\text{O}$ in the serum is also influenced by the so-called »chloride shift» when, as a result of an accumulation of carbonic acid Cl anions enter

¹ In this investigation the serum chloride amount has been expressed as a sodium chloride content.

the blood cells. The short-time circular stasis does not cause any noteworthy changes. BOENHEIM (1921) has also noted elevated values as a result of stasis. PETERS, BULGER, EISENMAN and LEE (1926) observed only negligible changes after a one minute stasis.

Light physical work does not alter the chloride concentration of the serum. In connection with strong perspiration, instead, a larger excretion of alkali chlorides may take place through the skin than through the kidneys (HÖGLER and ÜBERROCK 1927).

A diet constantly rich in chlorides produces a rise in the NaCl content of the serum and correspondingly a low-salt diet a decline (cf. ESSEN, KAUDERS and PORCES 1923). GAMBLE, ROSS and TISDALL (1923) noted after complete fasting a reduction of the serum chlorides. They explained this as partly due to deficient nutrition, partly to the entrance of chlorine into the blood cells occasioned by the acidosis which is produced in the period of fasting.

In my investigations I found after about 1 ½—2 minutes venous stasis variable, either slightly reduced or elevated values, as can be seen from Table 3.

Physiological Changes of Chlorides

The physiological changes in the NaCl content of serum in normal individuals are small. A daily intake of 10—15 g. of sodium chloride has no effect on the chloride concentration, and 40 g. of NaCl consumed every day raises the chloride content of serum only to 630 mg. per cent (PETERS and van SLYKE 1937). After the meal the amount of serum chlorides often declines, which is due to an increase of the secretion of hydrochloric acid in the stomach (DODDS and SMITH 1924).

There is no mention in literature of the variations of the serum chlorides in the course of longer periods. Table 4 presents my investigations on 5 individuals on 6 days, except in one instance on 5 days. The variations, as can be seen, are comparatively slight.

SURVEY OF EARLIER STUDIES OF THE SERUM CHLORIDES IN INFECTIOUS DISEASES

REDTENBACHER (1850) was the first to establish hypochloruria as a condition especially characteristic of *pneumonia*. SALKOWSKI (1871) arrived at the same conclusion in his investigations and noted, in addition, an equal excretion of sodium and chlorine in the urine.

PEABODY (1913) studied the metabolic changes of inorganic substances in pneumonia patients. He found that with a decline in the NaCl excretion

of urine the concentration of the blood chlorides was reduced. After the crisis, when the NaCl excretion showed a rise, the serum chlorine had likewise increased. He also established an elevation of chlorides in the tissues in the precritical period. Of the remarkably numerous investigators who have recorded similar findings for pneumonia patients, McLEAN (1915), SHIRALA (1917), SUNDERMAN, AUSTIN and CAMAC (1926), PETERS, BULGER, EISENMAN and LEE (1926) may be mentioned.

SUNDERMAN (1929) stated that in a patient on an ordinary diet with a low NaCl content and without extra salt, the chloride excretion in pneumonia exceeded the intake of salt in the precritical period. This is especially noteworthy since, in these patients, the plasma chlorides often fall below the normal threshold for chloride excretion. When the patients were given sodium chloride (15—30 g. per day), retention of chloride occurred in the precritical stage of the disease and after the crisis an increase of the salt excretion even when the chloride balance was mostly positive. SUNDERMAN consequently concluded that the retention of sodium and chlorine need not necessarily occur during the precritical stage. Yet, in this period, the capacity of the body to store up chlorides is reduced when the intake of chlorides is low. The capacity to excrete chlorides is likewise diminished when there is a large intake of chlorides. He also noted that the amount of NaCl in the expectorations and perspiration of the pneumonia patients was too low to cause a reduction in the plasma chlorides. The same view has been put forward by WILDER and DRAKE (1929), who also made a special study of water retention during fever. GREENWALD (1931) maintained that the earliest stage of pneumonia is characterized by a markedly large excretion of salt. He believed this to result in a reduction of the serum and urinary chlorides. IPSEN (1936) claimed that in lobar pneumonia the decline of chlorides was dependent upon the extent of the pneumonic process. LAUTROP and MADSEN (1942) studied the effect of sulphonamid preparations and a specific serum on chloride retention in pneumonia patients. They found that treatment with medicine had no effect.

In other acute infectious diseases — excepting diphtheria and also otitis media — chloride metabolism, according to the literature, has not been studied as systematically as lobar pneumonia.

REDTENBACHER as early as 1850 and SALKOWSKI (1871) were among the first to draw attention to the chlorine retention occurring in various febrile diseases such as exanthematous and abdominal typhus, erysipelas, recurrent fever, scarlatina and morbilli. However, the retention is not as considerable as in the lobar pneumonia patients. SIEDEK and ZUCKERKANDL (1935) noted correspondingly somewhat reduced values in acute hepatitis, CHRISTENSEN (1938) in otitis media and DIECKHOFF (1939) especially in diphtheria.

LAUTROP and MADSEN (1942) made investigations, except in pneumonia patients, also in other infectious diseases, in a total of 20 cases. The patients who had measles generally yielded normal values. Of three

angina cases one displayed hypochloremia in an early phase of the disease. Hypochloremia, the lowest value being 320 mg. per cent of Cl, was present, likewise, in one of the three scarlatina patients since the third week of the disease. This patient suffered from co-existent myocarditis and arthralgia. In influenza and infectious mononucleosis as in acute hepatitis the values were mainly normal or very slightly reduced. Influenza accompanied by encephalitis, on the other hand, and one case of meningitis showed markedly reduced values (305 and 320 mg. of Cl per 100 cc). In a patient affected with febris undulans the serum chloride concentration was normal in the 6th and 7th weeks in spite of continuous fever (38—40° Cels.).

L. KALAJA (1945) noted reduced chloride values of the total blood in various different infectious diseases. Hypochloremia was thus present in 7 out of 16 cases of septic infection, in three out of 20 cases of influenza, in one of 15 cases of acute hepatitis and in two cases of acute pancreatitis. He observed, in addition, in some cases with a low chloride concentration, an elevated non-protein nitrogen. RISKÅ (1945) studied the urine chlorides in pleuritic patients. Even considerable hypochloruria was encountered in some instances.

As a *summary* of the results obtained by the investigators mentioned in the foregoing we may say that among *acute infectious diseases* lobar pneumonia is the condition in which hypochloremia occurs frequently during the febrile period. The serum chlorine may fall even considerably below 300 mg. per 100 cc., and values between 300 and 320 mg. per 100 cc. (495—528 mg. of NaCl per 100 cc.) are not infrequent. Following crisis the chloride concentration rises to the normal level in 3—4 days. When resorption begins and with a gradual increase of the chloride content, values even exceeding the normal may occur. Along with a decline in hypochloremia the excretion of urinary sodium chloride is reduced, often to such an extent that the qualitative NaCl test of urine with silver nitrate is barely positive. In bronchopneumonia, influenza pneumonia and tuberculous pneumonia the chloride retention is markedly less.

In diphtheria, likewise, severe hypochloremia is often the case, as was pointed out by DIECKHOFF, *inter alia*, in his investigations. In other acute infectious diseases hypochloremia may occur especially in connection with the fever at the onset of the disease. Yet it is less marked in character than in pneumonia and diphtheria. Considerable variations may be observed in the hypochloremia even in the same disease group, and in infectious diseases it is often clearly dependent upon the severity of the disease and possible complications. Fever, on the other hand, does not always seem to play a decisive rôle in the reduction of the chloride concentration.

Before the sulphonamide preparations were introduced in the treatment of pneumonia, a number of investigations were made with a view of attempting treatment of these patients with NaCl or CaCl₂ (WILDER

and DRAKE 1929, McCANCE 1936 et al.). Though opinion was undivided as to the therapeutic effect of the treatment, certain theoretical aspects gave rise to doubts. All investigators had noted disturbance of the chloride balance and found that though sodium chloride is taken and some of it is retained in the tissues, such conditions as e.g. hypochloruria cannot be permanently abolished. A certain danger of oedema is also present, if too large amounts of salt are administered.

The reason for the *retention of chlorine and sodium* in pneumonia and in certain other acute febrile infectious diseases has not yet been fully elucidated. An increase of especially the chlorine and sodium amounts in the organism has been demonstrated. This increase in the chloride content of the organism, a diet low in salt, relative inanition and the increased loss of NaCl in vomiting, perspiration and expectorations do not sufficiently account for the hypochloremia. It is not improbable that one of these factors may have a contributory share in the development of this condition.

Some theories attribute hypochloremia to the passage of electrolytes between the tissue fluid and blood. According to HOLTEN (1926) the most essential factor in this phenomenon is the accumulation of organic acids in the tissue. DIECKHOFF, among others (1943), put forward the view that in all severe infectious diseases «transmineralization» is a prevailing phenomenon. It occurs in the presence of a condition in the tissue which is described by EPPINGER (1935) as «seröse Entzündung» and is characterized by the appearance of plasma protein in the spaces between tissues as a consequence of an increased capillary permeability. Due to a change in capillary permeability the electrolytes N^+ , Ca^{++} and Cl^- and fluid pass from the blood into the tissue, the electrolytes K^+ and PO_4^{--} being conveyed from the tissue into the blood. This «transmineralization» is accounted for by the accumulation of acids, and abnormal combustion results in the tissue. DIECKHOFF had noted, moreover, in connection with the flowing of the electrolytes, a reduction in the circulating plasma amount. As the red cell count and the blood haemoglobin rose, at the same time, the reduction in the plasma quantity must have been due to the fact that it flowed through the blood vessels. Of the numerous other investigators who have explained hypochloremia as being due, in infectious diseases, to disordered electrolyte metabolism, may be mentioned SIEDEK and ZUCKERKANDL (1935); JENSEN (1942); L. KALAJA (1945) et al.

According to EPPINGER the «seröse Entzündung» is a relatively common phenomenon in various diseased conditions which produce increased capillary permeability, thus also in several infectious diseases.

Some investigators have also noted, in hypochloremia, a rise in the *non-protein nitrogen*. BLUM, GRABAR and VAN CAULAERT (1928) drew attention to the existence of hypochloremia and extrarenal uremia in a number of various diseases (Azotémie par manque de sel). It was earlier supposed that the elevated non-protein nitrogen compensated the reduction in the osmotic pressure due to the chloride deficiency. Later investi-

gators, however, were able to demonstrate that the share of the non-protein nitrogen in maintaining the osmotic pressure is not of sufficient practical importance compared with that of the electrolytes. The increase of the non-protein nitrogen in connection with disturbed kidney and liver function is a recognized fact. L. KALAJA (1945), who in his investigations noted an elevated non-protein nitrogen in some acute infectious diseases, ascribed it to disturbed metabolism occasioned by injury to the capillaries.

In spite of a normal serum chloride concentration the urine may, according to LEHMANN (1944), indicate a deficiency of salt in the organism by a practical lack of NaCl. He points out that in these cases the kidneys store up the sodium chloride in the blood with a view of maintaining the normal level of the osmotic pressure. There is a considerable variation of the urinary chlorides, 2—3 g. being still indicative of a normal salt balance in the organism (PAINE and ARMSTRONG 1939).

According to the literature it is only in pulmonary tuberculosis, of the *chronic infectious diseases*, that chloride metabolism has been investigated systematically. Since BIERNACKI (1894) first noted reduced serum chloride values in this disease, numerous detailed studies have been carried out. The frequent occurrence of disturbances in the chloride metabolism has been established. Yet the investigators do not seem to agree as to the reasons for the hypochloremia present. BOENHEIM (1922), *inter alia*, claimed that the NaCl content of serum in pulmonary tuberculosis is dependent upon the stage of the disease and that mild and convalescent cases exhibit even values exceeding the normal. MÜLLER and QUINCKE (1927) noted both normal and clearly reduced values. In 4 severely affected patients out of their 30 cases the NaCl content of serum was below 500 mg. per 100 cc., in 16 the values varied between 500 and 550 mg. per 100 cc., the rest of the values being normal (the lowest limit 560 mg. per 100 cc.). HEILMEYER (1927) explained hypochloremia as due to acidosis, which MÜLLER and QUINCKE, however, were unable to confirm. The two last-mentioned, as several earlier investigators, observed an increase of chlorine especially in the body musculature. They attributed this to the fact that tuberculosis and the derangements caused by it had their own specific way of affecting the chlorine metabolism and the fluid economy. Eight out of the 10 cases of pulmonary tuberculosis and pleuritis reported by SUNDERMAN, AUSTIN and CAMAC (1928) exhibited hypochloremia. It was, however, of a much milder type than in the pneumonia patients. They explained the hypochloremia present in tuberculosis and in other febrile infectious diseases as not improbably due to metabolic disturbances, which, however, are less marked than e.g. in pneumonia.

SIDELIN (1934) examined over 50 patients with pulmonary tuberculosis. Of 18 severe cases 11 showed serum chlorine values under 330 mg. per 100 cc. In two cases with co-existent tuberculous meningitis and vomiting the serum chlorine was below 300 mg. per 100 cc. He recorded as his view that the chlorine concentration is generally lower in a tuberculous organism than normally.

Of chronic suppurative pleuritis I have encountered only one case in literature, examined in connection with the studies of fluid balance made by COLLIER, DICK and MADDOCK (1936) in surgical diseases. This patient had an opened chronic empyema and the plasma chlorides were somewhat reduced (554 mg. per 100 cc.).

OWN INVESTIGATIONS ON CHANGES IN SERUM CHLORIDE CONCENTRATION IN CASES OF CHRONIC EMPYEMA OF THE PLEURA

As appears from the review of the literature, elevation of the non-protein nitrogen has been noted in connection with hypochloremia. Notwithstanding the normal amount of serum chlorides NaCl has sometimes been found to be practically non-existent in the urine. In view of these findings I also undertook, in my investigations, determinations of the non-protein nitrogen and the urinary chlorides.

The results of these investigations in Cases 1—21 are presented graphically in Fig. 6—10 and those in Cases 22—59 in Table 5. The graphical figures are accompanied by tables showing the non-protein nitrogen and the NaCl content of the urine in the examined cases. The chloride investigations were made after operations in the same cases as those on proteins.

Considerable variations occurred in the serum chloride concentration in cases of chronic pleural empyema. While hypoproteinemia was not present before operation, hypochloremia occurred comparatively often. Taking into account, in each case, the values of the serum chlorides when the patient was admitted to hospital, or the first value independent of operations for those who were under clinical treatment when the investigations were started, we note that the serum chlorides ranged from 500 to 529 mg. per 100 cc. in 6 patients and 530—559 mg per 100 cc. in 19 cases. Among the normal values the serum chloride content was below 595 mg. per 100 cc. in 25 cases and above in 9 cases. The cases with a normal serum chloride concentration had a total empyema cavity in 8 instances (Nos. 3, 11, 27, 36, 43, 48, 56 and 57). In 4 of these cases (Nos. 3, 27, 36 and 43) various different operations had been undertaken before the first examination. In cases with a total cavity and when earlier no other operations had been carried out except

SERUM CHLORIDE CONTENT IN CASES OF CHRONIC EMPYEMA OF THE PLEURA
(CASES 1—21; FIGURES 6—10)

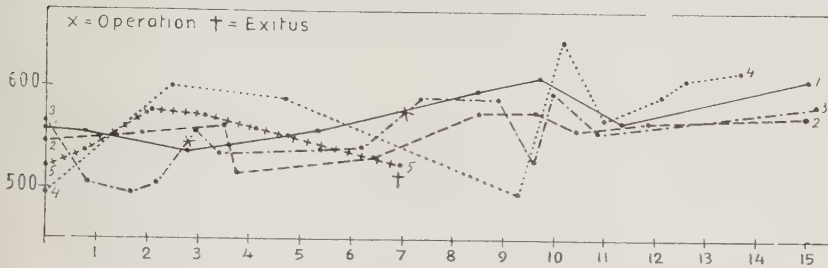


Fig. 6. — Cases 1—5. Ordinate: Serum chloride concentration (expressed as mg. of NaCl per 100 cc.).
Abscissa: Time in months.

Table to Figure 6

Non-protein Nitrogen of Whole Blood and NaCl Content of Urine in
Cases 1—5.

No. 1	30	27	28.5	—	25	37.5	—						
16/7. 45	16.1	16.8	—	—	16.3	14.3	9.7	14.1	—				
No. 2	41	27	31	—	—	—	40	—	—	—			
18/6. 45	3.9	8	7.3	—	11.9	9.2	4.7	10.5	5.2	7.7			
No. 3	30	29	28	26	—	—	—	—	—	—	—	—	—
2/7. 45	10.5	9.5	4.1	8.9	5.2	—	8.5	5.7	10.7	6.8	—		
	—	—	—										
	6.8	—	—										
No. 4	—	25	—	—	26	—	—	—	—	—			
1/5. 45	—	10.3	—	5.6	29.4	10.4	10.5	12.9	6.3				
No. 5	35.3	31.5	—	—	32.3	26							
4/7. 45	—	11.3	5.6	4.9	—	1							

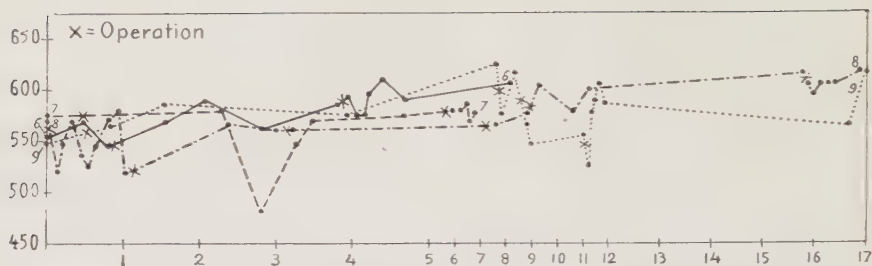


Fig. 7. — Cases 6—9. Ordinate: Serum chloride concentration (expressed as mg. of NaCl per 100 cc.).

Abscissa: Time in months.

Table to Figure 7

Non-protein Nitrogen of Whole Blood and NaCl Content of Urine in Cases 6—9.

No. 6	30	36	30	—	—	—	31.5	25	—	—	—
9/1. 46	—	—	2.6	5.8	11.9	23.6	4.9	2.5	4.3	7.1	—
	—	—	—								
	10.2	6.9	4.7								
No. 7	—	—	30	31	27.2	26	28.5	—	—	34.1	37.5
1/2. 46	1.4	6.8	5.8	10.2	6.8	9.1	4.6	5.8	10.4	8.9	7.7
No. 8	39	—	—	—	—	—	—	—	31.5	—	—
29/6. 45	7.8	—	—	—	—	—	—	—	5.1	—	—
	31	—	31	25	—	—	—	—	22	34	—
	8.8	16.2	9.8	30	9.8	13	7.8	10.5	13	15.7	7.3
	—	—	—								
	7.1	7.5	24								
No. 9	40	33.3	30	35.3	—	—	—	—	—	—	—
2.7. 45	8.2	12.6	3.6	11.2	6.6	2	12.6	2.5	3.1	17.7	14.6
	—	—	—	—	—	—	—	—	—	—	—
	6.1	3.9	14.6	8.5	14.8	14.8					

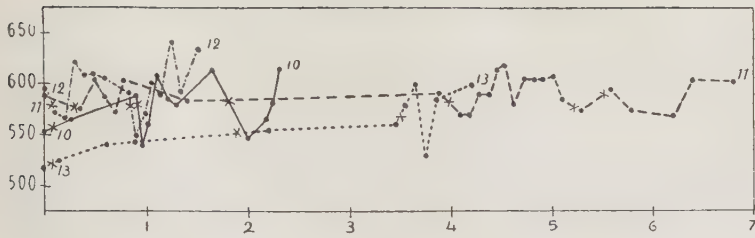


Fig. 8. — Cases 10—13. Ordinate: Serum chloride concentration (expressed as mg. of NaCl per 100 cc.).

Abscissa: Time in months.

Table to Figure 8

Non-protein Nitrogen of Whole Blood and NaCl Content of Urine in Cases 10—13.

No. 10	26	—	—	—	—	—	—	—	—	—	—	—
18/2. 46	1.5	15.6	6.2	13.8	6.2	18	2.2	7.4	34.4	28.5	5.5	—
	—	—	—	—	—	—	—	—	—	—	—	—
	4.7	1.6	—	4.5	—	—	—	—	—	—	—	—
No. 11	—	—	—	—	—	—	—	—	28.5	—	—	—
17/5. 46	15.3	1.4	5	10	9.1	—	10.3	14.6	2.3	—	1.5	—
	—	—	—	—	—	—	—	—	—	30	—	—
	2	3.1	5.6	5.4	5.6	4.3	9.9	8.7	12.9	9.9	4.4	—
	—	—	—	—	—	—	—	—	—	—	—	—
	1.2	3	7.8	5.8	—	—	—	—	—	—	—	—
No. 12	31.5	—	—	—	—	—	—	—	—	—	—	—
13/4. 46	6.3	1.6	0.7	7.7	12.7	10.8	14	6.5	5.6	0.8	1.9	—
	—	—	—	—	—	—	—	—	—	—	—	—
	13	18.7	11.4	10.9	—	—	—	—	—	—	—	—
No. 13	—	40	—	—	—	—	—	—	—	—	—	—
3/12. 45	23.1	5.6	10.7	16.5	16.1	—	3.4	11.3	15	5.5	14	—

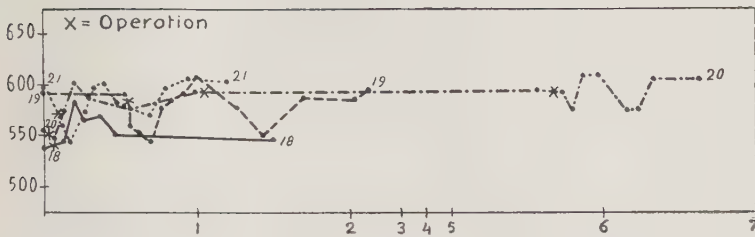


Fig. 10. — Cases 18—21. Ordinate: Serum chloride concentration (expressed as mg. of NaCl per 100 cc.).
Abscissa: Time in months.

Table to Figure 10

Non-protein Nitrogen of Whole Blood and NaCl Content of Urine in Cases 18—21.

No. 18	37.5	37.5	—	—	—	—	—	—	—	—	—	—
12/3. 46	5.5	8.3	5.7	6.5	10.7	13.2	—	—	—	—	—	—
No. 19	28	28.5	27.2	—	—	—	—	—	—	—	—	—
16/9. 46	10.9	14.6	4.7	9	6	0.8	13.8	4.5	1.8	13.1	4.8	—
	7.5	3	4.7	—	—	—	—	—	—	—	—	—
No. 20	—	—	—	—	—	—	—	26	50	50	—	—
14/5. 46	2.5	2.7	10	9	15.3	13.2	—	14.4	6.8	1.5	1.9	—
	8.5	10.4	5.3	14.5	7.8	—	—	—	—	—	—	—
No. 21	40	38	—	—	—	—	—	—	—	—	—	—
26/10. 46	12.9	2.1	1.2	3.7	5.1	12	7.6	21.8	11.5	15.8	30.6	—

thoracostomy, hypochloremia occurred in three instances out of 10 (Cases 5, 13, 50). In three cases, in addition, (Nos. 28, 29 and 47) the values were at the minimum normal level. The lowest serum chloride content in these cases was 518 mg. per cent (Case 13), and the highest 610 mg. per 100 cc. (Case 57). The size of the empyema cavity thus seems to have no decisive effect on the concentration of the serum chlorides.

The patients whose serum chlorides ranged from 500 to 529 mg. per 100 cc., were often in an extremely serious clinical condition. Thus in Case 26, where the chloride concentration was 501 mg. per 100 cc., the general condition was very poor. The case was, moreover, complicated by amyloidnephrosis. The cavity was total and opened and there was an abundant purulent discharge. In Case 25, on the other hand, where the amount of chlorides was almost as markedly reduced (503 mg. per 100 cc.), the empyema cavity was comparatively small. In this case mediastinitis was the complication present, due to which gastrostomy had been performed, and in addition pericarditis with a constant fever for about 3 months. In Case 49, where the amount of chlorides was 508 mg. per 100 cc., the lateral empyema cavity was of medium size, with a suppurative fistula leading to its lower part. Case 13 was similar in nature, and showed a chloride content of 518 mg. per 100 cc., but had a total cavity. In Case 24 the patient had earlier undergone operations because of a total cavity. About 5 $\frac{1}{2}$ weeks after the last operation, while the operative wound was suppurating continuously, the serum chloride content was 512 mg. per 100 cc. about one week before death. In Case 5 the cavity was total and a drain was introduced to its bottom section. The amount of purulent discharge from the pleura varied from 100 to 375 ml. in 24 hours. In the first examination, when the patient had fever, the chloride concentration was 521 mg. per 100 cc.

Among 19 cases with comparatively mild hypochloremia varying between 530 and 559 mg. per cent, Nos. 28, 29 and 52 had a total cavity. Due to thoracostomy they exhibited a suppurating fistula leading into the cavity, and the general condition was impaired. Two of the mentioned cases (Nos. 28 and 29) showed a value which was at the lowest normal level (559 mg. per cent). With a spacious fully opened cavity Cases 1 and 2 likewise exhibited mild hypochloremia (558 and 543 mg. per 100 cc.). The suppuration was com-

paritively abundant in these patients. Case 23 was in a condition following a total right-hand thoracoplasty, with a chronic bronchial fistula. Relatively large non-total cavities were noted in Cases 6, 10, 20, 38, 45, 47 and 50. Among these only the first was in a markedly poor general condition. In this instance the suppuration was also more abundant than in the rest. In Cases 9, 18, 31, 33, 42 and 44 the empyema cavities were small. Case 18 was tuberculous. A thoracoplastic operation had been carried out earlier because of a total cavity. In Cases 31, 38 and 50 the chloride values which were lower compared with the first examination, represent post-operative conditions. In Case 44, on the other hand, the patient was feverish during the second and third examinations.

In the cases examined regularly *after operation*, Nos. 6, 8—16 and 18—21 (Fig. 7—10) and 32 and 33 (Table 5), reduction of the serum chlorides was mostly noted. In three of these cases (13, 18 and 32) the chloride content remained unchanged after operation or was larger than before it. Other cases, instead, showed a variable reduction of the serum chloride content occurring almost regularly on the 2nd—4th days following operation. This decrease varied from 9 to 65 mg. per 100 cc. The pre-operative values were usually restored in from one to two weeks. Contemporaneously with the reduction in serum chlorides the NaCl content of urine showed a decrease. In Cases 17, 30, 36, 39, 40, 43 and 48, moreover, the reduced chloride values occurred after operations carried out.

The serum chloride concentration after different thoracoplastic measures in cases of chronic pleural empyema sometimes underwent marked variations even in the same patient and was evidently dependent upon the post-operative fever and the severity of the wound infection. Thus in Case 8 considerable hypochloremia was present, and the wound suppurated profusely still about one month after the first operation. After the last operation made, on the other hand, no noteworthy changes were observed, and the suppuration was less. In Case 11 the changes were negligible in two different operations (thoracostomy and decortication) in spite of the fact that in the former the pus formation and in the latter the haemorrhage were relatively abundant after operation.

I have not found any mention in the literature of investigations on post-operative serum chlorides in this disease. In numerous studies of both pre- and post-operative serum chlorides in association with operations

in the abdominal organs either unaltered or slightly reduced values have been established (KØSTER and TROLLE 1946; VARA and TIITINEN 1947 et al.).

After operations undertaken to remove the empyema cavity, we find the majority of the serum chloride values below 500 mg. per 100 cc. in *severe protracted wound infections*. The general condition of these patients was also markedly lowered. It is thus the severe cases 27 and 28 ending fatally that showed the lowest values occurring in my investigation, 418 and 423 mg. per 100 cc. The former case had, moreover, given reduced values (478 and 551 mg. per 100 cc.) in two examinations. In the latter case marked hypochloremia was present in three additional examinations (446, 495 and 511 mg. per 100 cc.). The lowest value occurred in Case 27 about 6 weeks after a performed operation and one day before death, in Case 28 correspondingly about 5 weeks after operation and about 3 weeks before death. Before operation the values were normal in both cases. Case 24, mentioned earlier, was similar in nature. In this patient the chloride concentration was in the first examination, about 7 weeks after operation and two weeks before death 486 mg. per 100 cc. and about one week before death 512 mg per 100 cc. after the administration of sodium chloride. The recently mentioned cases 5, 25 and 26, likewise terminated fatally. In Case 5, during continuous fever lasting about 4 months the serum chloride concentration was found to range between 521 and 577 mg. per 100 cc. in the five first examinations while the purulent discharge from the pleura varied from 100 to 375 ml. Values below 560 mg. per 100 cc. occurred in three examinations. About 7 months since the first examination the chloride content was 525 mg. per 100 cc. two days before death. The patient was then feverless. In Case 26 the total cavity had been opened about 4 months before the first examination and the suppuration still persisted. About 10 days before death the chloride content was 501 mg. per 100 cc. While in all the just mentioned cases the empyema cavity was total it was comparatively small in Case 25. During the fever the lowest chloride values observed in this patient were 503 and 516 mg. per 100 cc. With decline in the fever the chloride content rose to 586 mg. per 100 cc. and was 551 mg. per 100 cc. about 6 weeks before death.

Also in other cases of prolonged suppuration after operation markedly lowered chloride values were encountered as well as nor-

mal values. Thus in Case 1 six of the 10 examinations made in the course of about 15 months gave subnormal or clearly reduced values, the lowest of them being 510 mg. per 100 cc. In the tuberculous empyema case No. 2 the lowest value obtained in 10 tests made in the course of about 15 months was 516 mg. per 100 cc., and in 5 other examinations, in addition, subnormal or plainly reduced values were noted. The severe case No. 3, resembling the two former, had undergone several operations while the suppuration lasted. In 14 examinations undertaken in the course of about 15 months it was noted that the lowest values 495, 503 and 504 mg. per 100 cc. occurred while the patient had a temperature. Six other examinations, in addition, gave chloride values below 560 mg. per 100 cc., the lowest value being 530 mg. per 100 cc. In case 4, complicated by amyloid-nephrosis, fluctuating values were noted. Of 9 examinations performed in the course of about one year only two showed hypochloremia. The chloride content was then 495 mg. per 100 cc., the highest value noted in this patient being 636 mg. per 100 cc. In Case 7 where the general condition was at times much impaired and abundant suppuration took place, only two examinations during the 4 $\frac{1}{2}$ months when the patient was studied showed hypochloremia (479 and 548 mg. per 100 cc.). The lowest value occurred about 9 weeks after operation. Case 18 likewise exhibited hypochloremia (548 mg. per 100 cc.) still about 5 weeks after operation as did Cases 34 and 42 after about 5 and 6 weeks (553 and 532 mg. per 100 cc.) and Case 44 about 2 $\frac{1}{2}$ months after operation (546 mg. per 100 cc.). In Case 45 the chloride content was even approximately 2 months after the small operation undertaken 544 mg. per 100 cc.

Nothing corresponding to the »postinfectious hyperproteinemia» noted in connection with the protein investigations was encountered in the chloride examinations. In one case, indeed, (No. 32) the slightly elevated serum chloride content was 668 mg. per cent, which is the highest value that occurred in my investigations.

In the *chronic cases of bronchial fistula*, Nos. 23 and 54, hypochloremia was present in one examination. Case 22 also gave a value which was the lowest normal (561 mg. per 100 cc.). In this instance the serum chloride content rose when the fistulas closed, likewise in Case 23 along with an improvement in the general condition. In Case 54, on the other hand, which was tuberculous, a

reduction was noted in the NaCl content of serum when the general condition declined.

As I mentioned earlier, several investigators have established hypochloremia as a frequent condition in *tuberculous* patients. In my tuberculous chronic cases of empyema the serum chloride content varied from 495 to 610 mg. per 100 cc. Hypochloremia was present in 6 out of 10 cases (Nos. 2, 4, 18, 52, 54 and 55), whose general condition was poor. In three of these (Cases 2, 54 and 55), where investigations were carried out over a long period, a decline in the serum chlorides followed closely upon the decline in general condition. In one case (No. 57), where the serum chlorides were normal, the suppurating fistula leading into the empyema had existed for about 7 years.

Several earlier investigators have pointed out that in *febrile* infectious diseases, too, the NaCl content of serum is often reduced. In the chronic cases of suppurating pleuritis studied by me both normal and lowered values could be noted *during the fever*. Thus in Case 25 considerable hypochloremia was present while the temperature was elevated (305 and 316 mg. per 100 cc.), but when the fever vanished the values were higher (586 and 551 mg. per 100 cc.). This patient, it may be noted, had a gastric fistula at the same time, which evidently contributed in causing the hypochloremia. Cases 10 and 29 showed only negligible changes in the chloride content (553 and 559 mg. per 100 cc.). About one week after the fever had disappeared the latter case still showed very nearly the same value (562 mg. per 100 cc.). During the disease, in some patients, evident hypochloremia could be noted in association with a severe suppuration while the fever lasted, as in the cases 3 and 5 discussed earlier. Two examinations gave in Case 44 the lowered values 515 and 548 mg. per 100 cc. while there was fever. In two other examinations, when the fever had vanished, the hypochloremia also showed a decline (546 and 553 mg. per 100 cc.). In Case 55, likewise, the lowest chloride value occurred in an examination made in the febrile state. In one case, No. 12, on the contrary, the chloride content was normal during the fever (595 mg. per 100 cc.).

Comparative Material (Table 6)

In agreement with the cases of chronic empyema of the pleura the 30 cases in the comparative material showed marked variation in the serum

chloride concentration. The limit values which were in the former cases — taking into account all examinations — 418 and 668 mg. per 100 cc., were in the cases of the comparative material 436 and 653 mg. per 100 cc. (Cases 70 and 80). Values under 560 mg. per 100 cc. occurred in 13 cases. In one case (No. 62) the values were at the lowest normal level. Out of the 9 cases of bronchiectasis hypochloremia was present in two (Cases 60 and 67), and in three of the 9 patients with a pulmonary abscess (Cases 69, 70 and 71). Three patients with lung carcinoma gave normal values, but of the pulmonary tuberculosis cases (Nos. 81 and 82), one exhibited rather severe hypochloremia. Out of seven cases of acute pleural empyema 6 gave reduced values (Cases 83, 84, 85, 86, 87 and 88). The lowest of these values occurred in patients exhibiting a high fever and in cases where the general condition was conspicuously poor, and especially in the final stages of the disease evidently due, primarily, to cachexia, inanition and intoxication. In these instances nothing of special significance could be detected in the relation of non-protein nitrogen and the serum chlorides.

Discussion of Results

As is evident from the foregoing, hypochloremia is present in some cases of chronic empyema of the pleura, even when such low chloride values as must be attributed to possible fever or directly to operations and, especially, to tuberculosis, are left out of consideration.

In evaluating the reasons for the hypochloremia several factors must be taken into account. Thus, according to KIRK (1939), the following various factors, in addition to a diet deficient in salt, may account for the condition:

1. vomiting
 2. diarrhoea
 3. intestinal fistula
 4. abnormal excretion of salt in the kidneys
 - a) nephritis
 - b) diabetes mellitus (sodium and potassium disappear together with the ketone acids)
 - c) Addison's disease
 5. abundant perspiration
- AALKJÆR (1943) mentions, in addition, an abundant wound secretion.

When examining the reasons for hypochloremia, especially in the traumatic and metapneumonic chronic cases of pleural empyema one might feel inclined, when considering the just suggested various reasons, to attribute the condition primarily to a diet low in salt

or to an excessive loss of salt from the body in connection with the purulent discharge. The first-mentioned assumption, however, is contradicted by the observation that in some cases where hypochloremia was present the chloride concentration did not change in spite of the intake of physiological sodium chloride. It could in addition be noted that other cases — individuals on the same hospital diet and remaining under treatment for equally long periods — showed no reduction in the serum chloride content. It should also be mentioned that owing to war time conditions salt fish was a frequent dish at the hospital in the period in question. In a number of cases the hypochloremia disappeared after the intake of sodium chloride and the patient's general condition improved. It is, however, evident that in my cases, especially in the terminal stage of the disease, the impaired general health and inanition are partly responsible for the advancing hypochloremia.

The abundant wound secretion, on the other hand, seems to be a factor which should be taken into account when evaluating the reasons for the hypochloremia. No noteworthy perspiration nor vomiting was observed. The loss of chlorides through perspiration is negligible (DILL 1938). One patient had a gastric fistula (Case 25). Diarrhoea occurred only in some severe cases before death. Out of four cases complicated by amyloidnephrosis three (Nos. 4, 5 and 27) gave both normal and reduced chloride values. In one case (No. 26) with an opened cavity, severe hypochloremia was noted in the only examination undertaken. The lowest values occurred after operations made in connection with cases of prolonged wound suppuration, when the general condition was markedly poor. One patient with nephritis as a complicative condition (No. 9) showed no noteworthy changes in the serum chloride concentration.

However, the reduction in the serum chlorides does not seem to depend only upon the abundance of the purulent discharge, but also on the *severity of the infection*. When the former was comparatively slight, the serum chloride concentration was not infrequently normal even in cases with a large empyema cavity (e.g. Nos. 39, 48 and 57). In some cases, instead, reductions of a varying degree could be noted (Nos. 13, 28, 49 and 50). Yet of Cases 5 and 29, where the purulent discharge by the drain leading to the total cavity was distinctly more abundant than in the first-mentioned cases, only

the former showed any hypochloremia worth notice. In Case 11, likewise, though the purulent discharge was abundant, no hypochloremia was disclosed in any examination. In postoperative prolonged severe wound infections, instead, the hypochloremia was in a good many instances of a marked severity as compared with the cases just mentioned. The decrease in the serum chlorides, in these cases, often seems to be directly proportional to the severity of the infection or the toxic symptoms (Cases 1, 2, 3, 24, 26, 27, 28).

On the basis of what has been said in the foregoing it may be stated that in my cases the low salt content of the diet is not the primary reason for the hypochloremia. Nor does the amount of the purulent discharge issued in chronic infection always seem to contribute decisively to the reduction in the serum chlorides in hypochloremia cases. *In agreement with the findings of other writers in acute infectious diseases, I noted in several of my chronic cases that the main cause of hypochloremia may be explained by the damage to the capillaries and the consequent disordered metabolism.* The hypochloremia would then be only a symptom of the derangement in oxidation and metabolism. This conception is supported by the fact that in some cases, in spite of the administration of NaCl, the serum chloride content showed no rise and that the severest toxic symptoms were accompanied by the most marked reduction in the serum chlorides.

In the correlation of non-protein nitrogen and hypochloremia I was not able to find anything specifically noteworthy, not even in the severest cases of hypochloremia. In some instances changes falling within normal limits were present, with correspondingly higher values for non-protein nitrogen accompanying reduced chloride values. Yet even in the severest low chloride conditions (Nos. 27 and 28) the values of non-protein nitrogen were normal. Only in one case (No. 37) was the non-protein nitrogen slightly elevated (54 mg. per 100 cc.), but the serum chlorides were even then normal. Also after operation one case (No. 20) gave a slightly increased value (50 mg. per 100 cc.) while the chlorides remained normal.

The chloride content of urine showed marked variations in cases of chronic suppurative pleuritis. Yet the decrease in urinary chlorides usually occurred only contemporaneously with a decline in the

serum chlorides. Not in one single case was I able to confirm the observation recorded by LEHMANN (1944) that when there is a normal serum chloride concentration there was sometimes no NaCl in urine, which he took as a sign of negative chloride metabolism. The circumstance in question may have some clinical significance.

Summary

While no instances of pre-operative hypoproteinemia could be demonstrated, hypochloremia was present in several patients. Out of 18 cases where no thoracoplastic operations had been carried out earlier, but the cavity was closed or there was a suppurating fistula leading into it, 7 exhibited hypochloremia (below 560 mg. per 100 cc.). The lowest values were 508 and 518 mg. per 100 cc. In two of these instances the patient had fever at examination and one was tuberculous. Two, in addition, of whom one was febrile, gave values which were at the lowest possible normal level. The size of the empyema cavity did not seem to have any bearing upon the concentration of the serum chlorides.

In 13 of the 16 cases examined regularly after operation a reduction was noted in the serum chloride concentration. This occurred almost regularly on the 2nd-6th day after operation and varied mostly from 9 to 65 mg. per 100 cc. The normal pre-operative values were usually restored in the course of 1-2 weeks, but in connection with severe wound infections reduced serum chloride values could occur even later. Thus, in 18 cases of prolonged wound suppuration following operations undertaken to eliminate the cavity, hypochloremia of various degrees was noted in the course of 1-6 months. In several of these cases the values were below 500 mg. per 100 cc. The fever accompanying the wound infection was not infrequently found to enhance the hypochloremia. The lowest serum chloride values (418 and 423 mg. per 100 cc.), occurred in cases leading to death, in the final stage of the disease. The reduction of the serum chlorides often seemed to be directly proportional to the severity of the infection and the toxic symptoms.

In my opinion the hypochloremia is due to the the abundant wound secretion and especially to the disturbance in metabolism following upon damage to the capillaries caused by the severe chronic infection. In the severest cases cachexia and inanition then seem to be contributory factors.

No connection could be found between non-protein nitrogen and hypochloremia. Even in the severest cases of hypochloremia the amount of non-protein nitrogen was normal. Parallel with a reduction of the serum chlorides (also after operation) the urinary chloride showed a decline. I have not been able to corroborate in my investigations the suggestion made by LEHMANN that with a normal serum chloride concentration urine could be deficient in NaCl. In cases of tuberculous chronic empyema hypochloremia occurred in 6 out of 10 cases, the lowest value being 495 mg, per 100 cc. In cases of amyloid degeneration no outstanding divergencies could be noted in the serum chloride concentration compared with other equally severe suppurative cases.

VI

THE ALKALI RESERVE

ALKALI RESERVE IN NORMAL CASES

The normal values for the alkali reserve of venous blood, as recorded in the literature, show marked variation. Thus MÜLLER and ANTHERS (1927) regard 53—72 vol. per cent as limit values, the average being 58 vol. per cent. According to KIRK (1944) they range from 50 to 70 vol. per cent (22—30 millimols¹ per liter). BEST and TAYLOR (1945) mention a variation of normal values from 53 to 75 vol. per cent, while M. and O. BODANSKY (1944) regard 55—60 vol. per cent as the normal capacity of plasma to absorb CO₂. An alkali reserve above 70 vol. per cent is in their view indicative of incipient alkalosis. Only VARA and TITINEN (1947) in the literature I have been able to lay hands on, have made a fairly extensive study of the alkali reserve of normal individuals. In 50 cases in all, whose ages varied between 17 and 62 years, the alkali reserve of venous blood ranged from 42 to 66 vol. per cent. The mean value was 55.5 vol. per cent (± 0.74) and values under 50 vol. per cent occurred in 6 cases.

Own studies of normal individuals in ten cases are presented in Table 2. The lowest value was 52.6 and the highest 62.9 vol. per cent, the average being 58.7 vol. per cent. When considering the investigations recorded in the literature and my own, the values 40—75 vol. per cent may be regarded as normal.

Effect of Various Factors upon the Amount of the Alkali Reserve

Stasis brings about a reduction in the bicarbonate content of plasma (PETERS, BULGER, EISENMAN and LEE 1926).

Accumulation of CO₂ occurs, due to stasis, in venous blood. As the regular loss of CO₂ through the lungs is obstructed because of stasis, the compounds of bases and bicarbonate are not capable of neutralizing

¹ Vol. per cent of CO₂ = $2.3 \times$ millimol

the surplus acid formed. Further, in consequence of prolonged stasis, lactic acid is produced in the blood (DAUTREBONDE, DAVIES and MEAKINS 1923).

Heavy physical work and exertion also lead to acidosis, which is the result of an abundant formation of lactic acid in the body musculature (T. and W. PARSON and BARCROFT 1920).

GAMBLE, ROSS and TISDALL (1923) have noted that during fasting the bicarbonate content of serum is reduced. This is a consequence of the accumulation of organic acids in the blood.

After a $1\frac{1}{2}$ —2 minute circular stasis I noted in 10 control individuals regularly diminished values, as can be seen from Table 3.

Physiological Variations of the Alkali Reserve

Under normal conditions physiological factors such as e.g. sleep and digestion produce slight changes in the consistency of blood. Some time after the meal normal individuals show an elevation in the alkali reserve which is caused by an increased secretion of hydrochloric acid in the stomach (VAN SLYKE, STILLMAN and CULLEN 1917; KAUDERS and PORGES 1923 et al.) According to MÜLLER and QUINKE (1927) the daily variation in the bicarbonate amount may be 5—6 vol. per cent.

As is evident from Table 4, the alkali reserve, in my investigations, varied only slightly in the course of 6 days. The determinations were made partly in indifferent sick-cases.

SURVEY OF EARLIER INVESTIGATIONS ON CHANGES IN THE ALKALI RESERVE IN INFECTIOUS DISEASES

Among the infectious diseases of the lung, pneumonia is the condition in which the acid base balance of blood has been most frequently studied. The end-results of numerous investigations have shown that a reduction of the alkali reserve is the rule in pneumonia as in other febrile infections, though opinions differ regarding its degree and origin.

Even in *severe acute infectious diseases* the bicarbonate content of plasma in adult individuals is generally normal (WHITNEY 1917). However, in consequence of obstructed breathing changes occur not infrequently in the consistency of the blood gases of pneumonia patients, as was demonstrated by LUNDGAARD (1919), and MEAKINS and DAVIES (1920). The two last-mentioned authors, moreover, had observed marked acidosis in pneumonia. They carried out investigations on the carbondioxide capacity of arterial blood. The value compared with the average (52.7 vol. per cent) obtained

by them in determinations on normal individuals, was in cases of lobar pneumonia on an average 44.5 vol. per cent.

HACHEN and ISAACS (1920) and KOEHLER (1923) noted the reduction of the bicarbonate content of plasma during the high fever accompanying influenza and influenza-bronchopneumonia. HACHEN's and ISAACS' examinations of 20 severely affected patients showed in 4 cases a plasma bicarbonate concentration below 20 millimols (less than 46 vol. per cent), the lowest value being 10.4 millimols (24 vol. per cent). KOEHLER found, besides, that when the bicarbonate decreased, there was a corresponding change in the blood reaction.

STADIE and MARTIN (1924) had found that every degree of heightened temperature was reflected in a change in the blood bicarbonate content and correspondingly in the blood reaction. This amount, according to them, when the temperature rises 1°C (above 38°C) is $-0.022\text{ p}_{\text{H}}$. STADIE, AUSTIN and HOWARD (1926) attributed the decrease in bicarbonate content occasioned by the heightened fever to two reasons. In the first place the solubility coefficient of CO_2 shows a sudden fall along with a rise in temperature so that in a fever of 45° the physically dissolved CO_2 content is much lower than when the temperature is 38°C . The second contributory factor is the change in the dissociation standard of the acid group of blood proteins, especially haemoglobin.

HASTINGS, NEILL, MORGAN and BINGER (1924) used a reliable method (VAN SLYKE) in their extensive studies. They report a normal or only slightly reduced plasma bicarbonate value in lobar pneumonia and bronchopneumonia. Acidosis was not encountered. These authors declared that the respiratory mechanism is fully capable of sustaining the normal reaction of blood. On the basis of their findings they also maintained that alkali therapy was contraindicated in all the examined cases of pneumonia.

PETERS, BULGER, EISENMAN and LEE (1926) found the bicarbonate content of plasma, in lobar pneumonia, usually normal. In seven cases the lowest value was 50.7 vol. per cent while in the rest it varied between 54.7 and 66.5 vol. per cent. In two bronchopneumonia patients the bicarbonate content of plasma was 43.1 and 50.1 vol. per cent. The authors declared that in febrile infections the bicarbonate is mostly somewhat reduced. This is due to the fever, which diminishes the CO_2 capacity of the blood. They attributed the smaller diminution in lobar pneumonia of the bicarbonate content than in other febrile infectious diseases to the fact that in pneumonia the decrease of bicarbonate is obstructed by the impaired state of the respiratory mechanism.

VARA and TIITINEN (1947), in their investigation, could not establish any changes in the alkali reserve of their pulmonary patients nor in the amounts of other blood gases. The alkali reserve of seven pneumonia patients varied from 50 to 52 vol. per cent, except in one case of bronchopneumonia, where the value was 46 vol. per cent. In one of the two cases of pleuritis the bicarbonate content of the plasma was under 50 vol. per cent.

GAESSLER (1930) and BØGGILD (1942) have, among several other investigators, demonstrated that in severe *septic and pyemic fevers* the decline in the alkali reserve can sometimes be considerable. GAESSLER noted in his studies that in locally restricted infections (adnexitis, parametritis, pelveoperitonitis) the alkali reserve was slightly reduced depending on peritonitic symptoms. The lactic acid content of the blood was in these cases normal. With the development of pyemic symptoms the alkali reserve was reduced and the amount of lactic acid was normal or slightly lower. In the septic conditions the corresponding changes were clearly more marked. When diffuse peritonitis developed as a complication, the alkali reserve showed the greatest reduction — below 35 vol. per cent of CO_2 . The concentration of lactic acid in the blood varied in these patients from 12 to 22 mg. per cent. BØGGILD noted in suppurative peritonitis, likewise, markedly reduced alkali reserve values, and treatment with sodium bicarbonate then led to favourable results.

Children often exhibit acidosis in association with pneumonia as with other febrile infectious diseases, especially otitis media, mastoiditis, scarlatina, acute bronchitis etc. The condition may sometimes be severe (below 10 millimols), as has been demonstrated by HARTMANN, PERLEY, BOSMANN, NELSON and ASHER (1938) and KIRK (1944) *et al.* in their investigations. In these severe cases of acidosis the authors just mentioned could notice the favourable effects of alkali therapy.

DRAGSTEDT (1920) and HIRSCH (1921), among others, made *animal experiments* on changes in the alkali reserve in acute infections. Both investigators noted a decrease in the blood alkali reserve in these cases. HIRSCH injected intravenously into rats a solution containing different pathogenetic bacteria. About 2—4 hours after the injection a marked reduction in the alkali reserve took place, to the extent that the CO_2 vol. per cent which was 55 before the test could fall to 22. The decline in the alkali reserve seemed to be dependent upon the pathogenesis of the injected bacteria. In experiments where the infection had not abated sudden changes in the alkali reserve and irregular reduction were the rule.

SCHADE, NEUKIRCH and HALPERT (1921) noted the acidity of the tissue fluid in connection with inflammatory processes, the degree of the acidity being higher the acuter the inflammation.

HERRMANNSDORFER (1927) suggested in his thesis that patients with granulating wounds or a septic infection exhibited both a local acidosis of the tissue in the infected area and a compensated acidosis of the blood, leading to a marked decline in the alkali reserve. 13 cases in all yielded values ranging from 29.1 to 48 vol. per cent. In 6 cases the alkali reserve was under 40 vol. per cent, and in two of them they fell below 30 vol. per cent.

In his view local and general acidosis acts as a preventive and an important expedient of the organism in its fight against infection. He also pointed out that a high-acid diet led to an increased acidity of the wound secretion, which had the effect of promoting the healing of the wound and the patient's recovery.

HERRMANNSDORFER was the first to make clinical investigations of this nature in acute and chronic cases of wound suppuration. Yet the number of his cases is too small to warrant really trustworthy conclusions. The author himself considers the alkali reserve values occurring in suppurative infections low, but yet, even admitting possible errors of examination, he explains them, in the cases mentioned, as pointing to acidosis. He determined the alkali reserve by VAN SLYKE'S volumetric method.

Among chronic infectious diseases, investigations on the acid alkali balance have been conducted especially in pulmonary tuberculosis. HACHEN (1922) and SWEANY (1923), two American investigators, have especially distinguished themselves in these studies. HACHEN noted in 213 patients affected with pulmonary tuberculosis a variation in the alkali reserve values between 48 and 73 vol. per cent. The determinations were made by means of VAN SLYKE'S method. The urine reaction and the alkali reserve did not show similar changes. When the urine was acid, acidosis was not present. Along with a development of the disease a slow reduction was noted in the alkali reserve, but the author could never trace acidosis. HACHEN classified the tuberculous cases, from the mild to the severest types, into four groups. The following summary shows a decline in the alkali reserve accompanying a deterioration in the prognosis of the disease.

Stage of disease	1	2	3	4
Alkali reserve on an average	61.1	59.9	56.4	54.4

SWEANY in his extensive study confirmed HACHEN'S findings to the full by establishing normal alkali reserve values for pulmonary tuberculosis. They generally approached the lowest normal level.

MÜLLER and ANTHER (1927) record that out of 26 patients affected with pulmonary tuberculosis, on whom they had made about 50 alkali reserve tests, two gave the values 49 vol. per cent, and 43 vol. per cent, respectively, a few days prior to death. All the other values fell within normal limits (53—72 vol. per cent, according to the authors). They hold the view that the decline in the alkali reserve in severe cases of pulmonary tuberculosis is due to the acid results of the decomposition of the albumin substances. The alkali reserve shows decrease and is closer to the lowest normal. Yet actual acidosis is not produced. It is only in rapidly advancing cases of pulmonary tuberculosis leading to death that the alkali reserve falls to the lowest normal level.

COLLER, DICK and MADDOCK (1936) established in one examined chronic case of pleural empyema the alkali reserve value as 58 vol. per cent, and 56 vol. per cent in an acute case of elbow infection.

The *pathogenesis of acidosis* in cases of severe febrile infection or septic conditions has not been elucidated. However, it is probable that *anoxia* and *inanition* have a share in producing acidosis. The not infrequent rise in the lactic acidity of plasma in severe febrile infectious diseases has been

recognized, among others, by GAESSLER (1930) and HARTMANN (1938) and the associate of the latter. The acid substances formed in consequence of *intoxication* may promote the development of acidosis. The acidosis present in severe septic conditions may be regarded as a stage in the development of pre-mortal acidosis, which evidently is a result of the accumulation of organic acids in the blood. In these instances anoxia and the frequent terminal infection would contribute in bringing about acidosis (KIRK 1944).

Chronic inflammation and fibrosis in the interstitial tissue, diminished elasticity and other structural changes in the lungs may together cause even marked alterations in the respiratory gases. This may also lead to changes in the plasma bicarbonate values. I therefore find that a short reference to these conditions is not out of place.

HOOVER and TAYLOR (1915) found that in emphysema and in some cases of chronic bronchitis the CO_2 in the alveolar air and the bicarbonate concentration in the plasma had increased while the chlorides had declined. The observation has been corroborated by several other investigators (MEAKINS and DAVIES 1920; ESSEN, KAUDERS and PORGES 1923, et. al.).

These investigators explain the accumulation of carbonic acid in the blood as a consequence of a primary disorder in the respiratory mechanism due to a pulmonary disease. This is common in such diseases of the lung where mechanic obstructions to respiration occur and anoxia, cyanosis and dyspnoea are present. The increased CO_2 content of the alveolar air is counterweighed by an increased alkali reserve, which is compensated by a reduced serum chloride concentration, so that the total electrolyte content and the osmotic pressure remain normal.

In the literature at my disposal I have not met with records of extensive studies on the acid base balance in chronic suppurative infections, with the exception of the isolated cases of osteomyelitis examined by HERRMANNSDORFER, and one case of chronic empyema of the pleura reported by COLLIER, DICK and MADDOCK.

OWN INVESTIGATIONS ON CHANGES IN THE AMOUNT OF THE ALKALI RESERVE IN CASES OF CHRONIC EMPYEMA OF THE PLEURA

The results of my investigations in Cases 1—21 appear in Fig. 11—15. The graphical representation of the alkali reserve values covers some of my severest cases, which were under clinical treatment for nearly a year and a half. The findings in Cases 22—59 are shown in Table 5.

The alkali reserve values in chronic pleural empyema show comparatively small variations. For a clear conception of the alkali reserve in my investigation, the values obtained may be classified

ALKALI RESERVE IN CASES OF CHRONIC EMPYEMA OF THE PLEURA
(CASES 1—21; FIGURES 11—15¹)

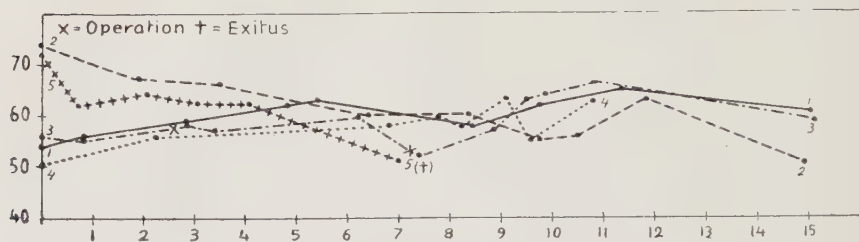


Fig. 11. — Cases 1—5. Ordinate: Alkali reserve (vol. per 100 cc.).
Abcissa: Time in months.

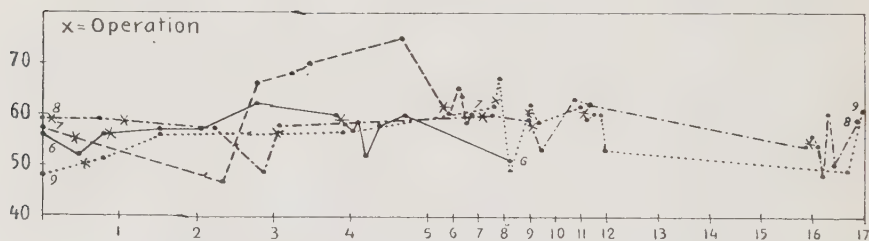


Fig. 12. — Cases 6—9. Ordinate: Alkali reserve (vol. per 100 cc.).
Abcissa: Time in months.

¹ The time when the first investigation in these cases was carried out was the same as that of the corresponding cases in Figs. 6—10.

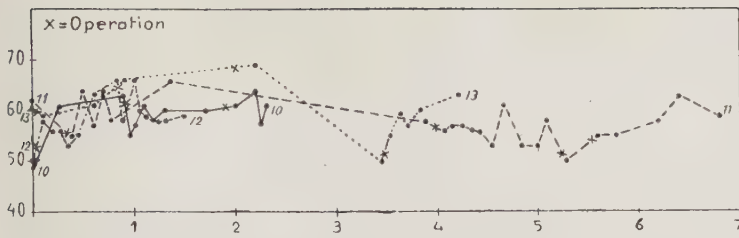


Fig. 13. — Cases 10—13. Ordinate: Alkali reserve (vol. per 100 cc.).
Abscissa: Time in months.

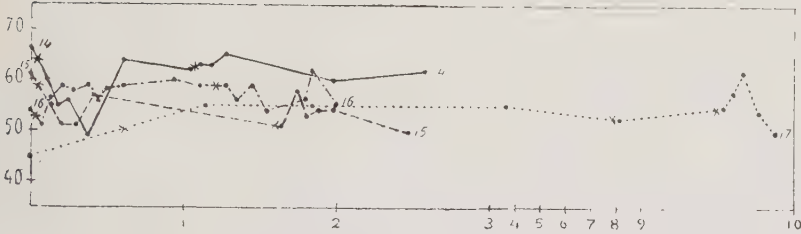


Fig. 14. — Cases 14—17. Ordinate: Alkali reserve (vol. per 100 cc.).
Abscissa: Time in months.

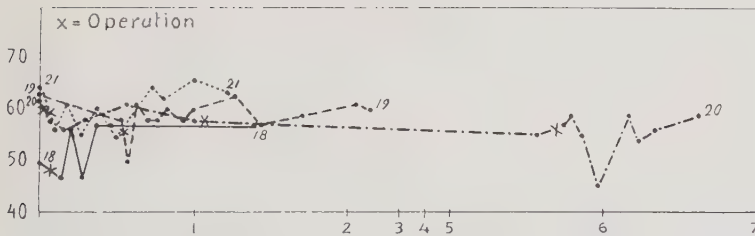


Fig. 15. — Cases 18—21. Ordinate: Alkali reserve (vol. per 100 cc.).
Abscissa: Time in months.

into distinct groups, as was done in the case of proteins and chlorides. The alkali reserve values established in the same examinations have been taken into account in the present classification. When evaluating the results it should, however, be noted that the clinical condition exhibited by the patients at the first examination varied markedly. Alkali reserve values falling below the average normal 58 vol. per cent mentioned by MÜLLER and ANTHERS (1927) — which is in keeping with the average of my own normal cases — occurred in 29 cases. In 8 of these the value was below 50 vol. per cent. In 30 cases the alkali reserve was 58 vol. per cent or more. The limit values were 43 vol. per cent (Case 41) and 74 vol. per cent (Case 2).

Out of the 8 cases where the plasma bicarbonate content was under 50 vol. per cent, five (Nos. 9, 17, 24, 26 and 41) had an opened suppurating empyema cavity. The period following operation, before the examination was undertaken, varied in these cases from 3 weeks (Case 41) to 4 months (Case 26). In three cases (10, 25 and 29) a suppurating fistula led into the cavity. Two of these patients had a rise in temperature (Nos. 10 and 25). A total empyema cavity existed in four (Nos. 10, 24 and 29), and albumin had been revealed in the urine of one (No. 26).

The serum chlorides of two patients (Cases 17 and 41), who in these examinations gave the lowest values (45 vol. per cent and 43 vol. per cent) were normal. In the rest of the cases where the alkali reserve fell below 50 vol. per cent, hypochloremia of varying severity was the rule (varying from 501—559 mg. of NaCl per cent). One case (No. 2) where the alkali reserve was 74 vol. per cent, exhibited co-existent hypochloremia. Thus there seems to be no special interrelation, in these examinations, between the alkali reserve and the serum chlorides.

In 18 cases where no other operations excepting thoracostomy had been made, or the empyema cavity was still closed, the lowest alkali reserve value was 49 vol. per cent (Cases 10 and 29) and the highest 72 vol. per cent (Case 5). The two first patients were febrile. A value under 58 vol. per cent occurred, among these 18 cases, in 3 additional instances (Nos. 12, 35 and 56) and the lowest bicarbonate content (50 vol. per cent) in a febrile case (No. 12). Two of the aforementioned cases (Nos. 29 and 56) had a total empyema cavity, likewise seven of the cases in which the alkali reserve was 58

vol. per cent or more (Cases 5, 8, 11, 13, 28, 48 and 52). The size of the empyema cavity thus does not seem to be of significance from the point of view of the alkali reserve value.

*After operations*¹ only negligible variations occur in the alkali reserve of 15 examined patients, as appears from the graphic charts 12—15, in Cases 6, 8—16, 18—21, and in Case 32 from Table 5. Yet most instances show a small shift in the acid base balance in the acid direction. In Case 12, who had a rise in temperature at the first examination, the values noted after operation exceeded the pre-operative value. In the rest of the cases the alkali reserve fell 7 vol. per cent, on an average, after operation. The lowest values generally occurred on the 6th—10th days after operation evidently depending, primarily, upon the severity of the wound infection and the abundance of the discharge (e.g. Cases 6, 9, 11 and 14). In two cases (Nos. 19 and 21) the values (50 and 56 vol. per cent) noted on the day following the operation were clearly reduced when compared with the pre-operative level (58 and 64 vol. per cent.) In both these cases there was fever. When the operative wound suppurated, irregularly decreased normal alkali reserve values were observed, and the pre-operative level was restored in about 1—4 weeks.

When considering the *reason for the post-operative decline* in the alkali reserve, *narcosis* and *inanition* should be given their due place. Several investigators have noted acidosis *immediately* following operation (ROSCHER 1933; VARA and TITINEN 1947 et al.). Ether, especially, tends to disturb the metabolic processes. The oxygen combining power of the red cells is upset or the ether causes toxic injury to the tissues, which are rendered incapable of receiving oxygen. One consequence of this is a rise in the lactic acid content of blood (RONZONI, KOECHIG and EATON 1924). Very mild post-operative acidosis may also follow anaesthesia with novocain (ANTONIN 1931). The thoracoplastic operations were in my cases made under novocain anaesthesia, so that the post-operative changes were often evidently relatively small. Due to the local anaesthesia inanition, fasting observed on account of the operation is of no consequence in the estimation of my cases.

Further, the possible *psychic effect* produced by fear and the operation trauma should be considered, though as a less important and less frequent factor (ROSCHER 1933). How much is due to these factors will be difficult

¹As in the investigations on serum protein and chlorides, the first post-operative determination of the alkali reserve was mostly made on the second or third day.

to determine. Fear does not seem to have any noticeable effect in any of my cases. Some few patients manifest evident nervousness or restlessness before operation. Yet no marked divergencies can be observed in the ratio of the acid base balance compared with other cases.

TÖNNIS (1929) emphasizes especially, on the basis of his animal experiments, the significance of the *operation wound* itself and the resorption of the *wound secretion*, and also that of the protein split products in increasing the acid components of blood. In his experiments on dogs no lowering of the alkali reserve occurred until 16 hours after operation. My own observations, too, show unmistakably that the wound secretion has some share in the reduction of the alkali reserve. The acidosis due to narcosis usually occurs immediately after operation while, on the other hand, *in my own investigations, alkali reserve values reduced in comparison with the pre-operative level are noted even later when the operative wound is suppurating.*

Acidosis may also sometimes occur in consequence of abundant *haemorrhage*, as was shown by BENNET (1926) et al. In my investigations the haemorrhage was generally slight in character. In one case (No. 11), with a relatively abundant haemorrhage after operation, no marked changes could be established in relation to other cases. The *operative shock*, whose effect in producing acidosis is generally known (MENTEN and CRILE 1915 et al.) has likewise in my cases been of little importance, for the enhancing effect of the shock on acidosis is restricted to the period immediately following operation.

The *rise in temperature* accompanying operations itself increases acidosis. Cases showing a marked decline of the alkali reserve immediately after operation exhibit a contemporaneous rise in temperature. Most feverish patients, likewise, independently of the operations undergone, yield relatively low values compared with other examinations. Thus in Cases 10, 12, 25 and 29 the alkali reserve values obtained during fever vary from 47 to 50 vol. per cent. These amounts are among the lowest occurring in my investigations, together with the alkali reserve figures obtained in some cases before death. In two febrile cases (Nos. 5 and 44), however, no noteworthy changes were detectable in the ratio of the acid base balance.

Morphine sometimes produces in the organism a shift in the acid base balance first in the acid and later in the basic direction (SCHOEN 1923). In local anaesthesia with small doses the effect is negligible.

In cases of prolonged severe suppuration following operation the alkali reserve varied between 36 and 75 vol. per cent. In some instances when the removal of the whole lateral wall was necessary in order to eliminate the cavity, examinations were conducted during a whole year of clinical treatment. In these patients, too, the alkali reserve was normal, though irregular variations

occurred in the ratio of the acid base balance and, not uncommonly, reduced alkali reserve values compared with other examinations were noted.

In *fatal* cases the lowest value was 36 vol. per cent (Case 27). The general condition of this patient was very poor and the wound suppurated profusely. The disease was, in addition, complicated by amyloidnephrosis, and the urine albumin varied from 8 to 15 per mille (ESBACH). Before the operation the amount of the alkali reserve was 57 vol. per cent. The operation was followed by a severe wound infection, the general condition declined and the urine albumin showed an increase. About 3 weeks after the operation undertaken and 3 weeks before death the alkali reserve value was 36 vol. per cent. It is evidently a case of slight so-called nephrogenic acidosis. Severe diseases of the kidneys, as was first established by PALMER and HENDERSON (1915), are characterized by a diminished excretion of ammonia. Instead of ammonia the organism, in these cases, makes use of sodium and potassium to neutralize the excreted acids, which leads to a decrease of the total bases. In the case in question the serum NaCl (478 mg. per 100 cc.) showed an obvious decrease, but yet the NaCl content of urine was proportionately high (1.8 g.) This seems to imply that along with a decrease in the serum chlorides the capacity of the kidneys to store up chlorides declines. The phenomenon has been pointed out by PETERS, WAKEMAN, EISENMAN and LEE (1929) in reports on investigations.

In the other fatal cases, Nos. 5, 24, 25, 26 and 28, the limit values were 45 vol. per cent and 72 vol. per cent. The values recorded for the first of these patients varied during a febrile condition lasting for about 4 months from 62 to 72 vol. per cent. Two days before death, when albumin was obtained in the urine, the corresponding value was 51 vol. per cent. In Case 24, about 2 weeks prior to death, the alkali reserve was 47 vol. per cent, and one week before death 49 vol. per cent. The urine did not contain albumin. In Case 25, while the patient was feverish, the plasma bicarbonate content was 47 vol. per cent, and nearly 6 weeks later, about 6 weeks before death, 59 vol. per cent. Some albumin was also occasionally obtained in the urine. In Case 26 the only examination made about 10 days preceding death yielded 47 vol. per cent as the plasma bicarbonate value. A considerable amount of albumin was present in the urine of this patient. In the following case (No. 28) no urinary albumin

was disclosed. In the first examination, when a suppurating fistula led into the empyema cavity, the alkali reserve level was 57 vol. per cent. After the second operation a severe wound infection set in. The suppuration was profuse for over 6 weeks and the general condition declined. Six days before death the alkali reserve was 45 vol. per cent. In all the fatal cases mentioned, except in Case 25, the empyema cavity was total. Case 4, which also ended fatally about $1\frac{1}{2}$ years after the last examination, will be described more in detail later.

As can be seen from the foregoing, *a shift takes place in the acid base balance in the acid direction before death*. Compared with the rest of my material the majority of values falling under 50 vol. per cent occurred in these cases. Yet actual acidosis was established in only one case (No. 27), with co-existent severe amyloidnephrosis. The reason for this so-called «*pre-mortal acidosis*» has not yet been elucidated. However, BECHER, ENGER and HERRMANN (1932) have found a considerable increase in the blood acids dissolving in ether immediately before and after death. It is therefore probable that acidosis is a result of an accumulation of organic acids in the blood. In these cases both anoxia and infection seem to promote the development of acidosis. The tissue cells are primarily injured by intoxication, and abnormal organic and inorganic acids are formed in the consequent decomposition. This toxic condition also causes disturbances of the blood circulation and, in consequence of anoxia, accumulation of lactic acid occurs in the blood. In addition to the authorities just mentioned KIRK (1944) has established an increased amount of amino acids in the blood during pre-mortal acidosis.

In some cases of prolonged suppuration, studied in the course of rather long periods, it was noted that along with a lessened suppuration, the healing of the wound and an improvement in general health, the alkali reserve rose. Thus in Case 1, where the lateral wall of the total empyema cavity was completely eliminated, intermittent profuse suppuration continued for over a year. The alkali reserve, which was 54 vol. per cent at the first examination, was 66 vol. per cent about one year later. The wound surface was almost totally epithelialized and the general condition showed marked improvement. In Case 3, also, which was particularly severe, a slight tendency towards an increase of the alkali reserve could be

noted along with an improvement in the general condition and a gradual lessening of the suppuration. Yet even irregularly reduced values, in relation to other examinations, were encountered, the limit values being 52 and 66 vol. per cent. The same holds good of Case 7. About 7 weeks after operation the alkali reserve value obtained was 47 vol. per cent, and about 2 weeks before operation it was 57 vol. per cent. When the lowest value occurred, the patient was feverish, suppuration was abundant and the general condition markedly poor. In conjunction with a decrease in the wound secretion and an improvement in the general condition the alkali reserve was augmented and was after about 2 ½ months 75 vol. per cent, but it declined again after an operation carried out and when the wound was suppuring. Like the above mentioned cases, Case 4, affected with amyloidosis, and Cases 8, 9, 13 and 17 showed an increase in the alkali reserve when the patient was recovering. In Case 4 the limit values were 50 and 63 vol. per cent and in Case 8 respectively 49 and 63 vol. per cent. In Case 9 the values varied between 48 and 67 vol. per cent, in Case 13 they ranged from 50 to 68 vol. per cent, and in Case 17 between 45 and 62 vol. per cent. In the last-mentioned case the lowest value occurred about 3 weeks after operation, when there was retention in the wound and the suppuration was markedly abundant. The severe cases 10 and 45 displayed relatively slight changes. In the former case the first examination, when the patient was feverish, showed the alkali value 49 vol. per cent. This minimum value was evidently ascribable to the fever.

In cases 2 and 5, in addition, the continuous suppuration and the impairment of the general condition seemed to be accompanied by a decline in the alkali reserve. The first-mentioned patient, who was examined during a period of over one year, suffered from tuberculosis. The limit values in this cases were 74 and 50 vol. per cent (Case 2) and 72 and 51 vol. per cent (Case 5).

In cases of chronic bronchial fistula (Nos. 22, 23 and 54) the limit values were 54 vol. per cent and 68 vol. per cent. Case 22 displayed a rising tendency in the alkali reserve during the 10 months when the fistulas were closing (54, 62 and 63 vol. per cent). Case 23, where no healing of the fistulas took place during the examinations, gave variable values. In three examinations carried out in a 5 months' period the values varied from 59 to 67 vol. per cent. In

Case 54, affected with tuberculosis, the lowest values of the alkali reserve occurred when the general condition was declining.

Tuberculous cases of chronic empyema showed no significant divergencies in relation to the other cases. In a total of 10 cases the limit values were 50 vol. per cent (Nos. 2, 4 and 18), and 74 vol. per cent (No. 2). Only one, after operation (Case 18), had the values below 50 vol. per cent.

Comparative Material (Table 6)

Compared with chronic diseases of the lung and acute cases of suppurative pleuritis no noteworthy divergencies could be established in the ratio of the acid base balance in chronic suppurative pleuritis. The limit values of the alkali reserve, which were 36 and 75 vol. per cent in the last-mentioned condition, were in the cases of the comparative material 45 vol. per cent (Case 71) and 75 vol. per cent (Case 63). Values below 50 vol. per cent occur in 3 cases in all (Nos. 70, 71 and 87). The lowest values were noted either in a febrile state of the patient or when the general condition was very poor. In one case of pulmonary tuberculosis (No. 82) the alkali reserve level was seen to diminish, with a decline in the general condition, from 58 vol. per cent down to 50 vol. per cent.

Discussion of Results

It appears from the foregoing, *that several cases of chronic empyema of the pleura showed in association with prolonged wound infection and abundant suppuration after operation changes within normal limits in the acid base balance of the organism. A slight shift in the direction of acidosis was then manifested.* This shift usually coincided with abundant suppuration. With a decrease in the wound secretion the alkali reserve showed a rise. *The reason for the reduction in the alkali reserve, it would seem, should be sought for in the severe infection and the abundant wound secretion.* The acid substances formed in consequence of a severe intoxication would then further the development of acidosis as do the disturbances in blood circulation and anoxia. It is possible that due to the abundant acid wound secretion local acidosis of the tissue is caused in the inflamed area. This would result in compensated acidosis of the blood with consequent decline in the alkali reserve, as was suggested by HERRMANSDORFER (1927), et al. Rise in temperature occurred rarely, but when co-existent with suppuration it tended to further, in my cases, the reduction in the alkali reserve.

After operations, in examinations mostly made every second day, beginning with the second or third post-operative day, the changes noted in the alkali reserve level were negligible and in the majority of instances within the limits of possibilities of error. The cases showing a marked reduction of the alkali reserve immediately after operation exhibited co-incident fever, which was evidently of especial significance. The slight post-operative alterations were in many cases, primarily, due to the fact that the examinations had generally not been made until the second day following operation, and secondly to the novocain anaesthesia. ANTONIN (1931), among others, has established that the post-operative changes in the acid base balance of the organism are negligible and often within the limits of possibilities of error.

The finding reported by HERRMANSDORFER that acidosis of the blood is a condition accompanying granulating wounds, has not been confirmed in my investigations. On the contrary, in my cases the alkali reserve showed a gradual rise when the wound was healing. In Case 1, for instance, during the process of granulation in an extensive wound surface lasting for several months, the lowest noted value, 54 vol. per cent, occurred when the suppuration was most abundant, while all the other examinations yielded higher values. Case 4 was similar in character. In Cases 42 and 59, likewise, when the empyema cavity was closing and granulating after operation, the alkali reserve values were 63 and 55 vol. per cent.

Summary

In chronic cases of empyema of the pleura the the alkali reserve level was normal, regardless of the size of the empyema cavity. After operations, the first determination mostly made on the second post-operative day, slight changes occurred in the acid base balance simultaneously with wound infection. In 14 out of 15 cases examined the average reduction in the alkali reserve was 7 vol. per cent. In one case with a rise in temperature before operation, the post-operative values were higher than the pre-operative. When the wound supplicated, the lowest values were obtained about 6—10 days after operation. In severe suppurating conditions lasting for several months and even over a year variable alkali reserve values were noted. Some patients whose general condition was declining showed an accompanying

TABLE 6 (COMPARATIVE MATERIAL)

SERUM PROTEIN AND CHLORIDES (NaCl), ALKALI RESERVE AND THE VITAMIN C CONTENT OF SERUM IN SOME CHRONIC DISEASES OF THE LUNG AND CASES OF ACUTE EMPYEMA OF THE PLEURA

The haematocrite value (vol. %), haemoglobin (Sahli), the red cell count (in millions) and the non-protein nitrogen also appear in the Table.

No.	Case record	Sex	Age	Diagnosis	Date of test	Protein %	Chlorides mg %	Alkali reserve vol. %	Vitamin C mg %	Haematocrite	Haemoglobin	Erythrocytes	Non-protein nitrogen mg %	Urine		Remarks
														Alb. 0/00	NaCl	
60	40/II.46	♀	23	Bronchiectasiae pulm. l.d. Broncho-pneumonia pulm. l.a.	25/9. 45 10/10. 45 6/2. 46 21/3. 46 12/4. 46 21/12. 46	7.5 7.7 6.4 6.7 8.1 6.9	559 529 536 562 594 572	73 73 62 61 64 65	0.32 0.46 0.34 0.37 0.54 0.21	33	60	3,350	33	—	7.2	General condition impaired. Intermittent temperature. Amount of sputum varying from 100 to 500 ml. per day.
61	2/II.47	♀	34	Bronchiectasiae lobi inf. pulm. l.a.	18/4. 46	8.0	578	64	0.54	—	67	4,230	—	—	—	General condition fair.
62	910/II.46	♀	31	Bronchiectasiae pulm. l.d.x.	11/5. 46	7.3	559	61	0.26	—	74	4,600	28	—	4.5	General condition impaired. Amount of sputum ab. 100—300 ml. per day.
63	944/II.46	♂	36	Bronchiectasiae pulm. l.a.	22/5. 46	7.5	584	75	0.20	32	73	3,950	—	—	—	General condition fair.
64	3/II.47	♀	—	Bronchiectasiae lobi inf. pulm.d.x.	15/6. 46	6.6	587	63	0.41	35	72	4,460	—	—	5.6	General condition good. Amount of sputum small.
65	1975/II.46	♂	31	Bronchiectasiae lobi inf. pulm. l.sin.	19/10. 46	7.6	587	60	0.29	—	83	4,790	30	—	—	General condition good.
66	2158/II.46	♀	53	Bronchiectasiae pulm. l.d.x.	19/12. 46	6.2	589	68	0.08	44	78	4,520	38	—	—	General condition fair.

67	190/II.46 ♀	36	Bronchiectasiae pulm. l.sin. Absces- sus pulm. l.sin.	18/1. 6/2.	46 46	6.1 6.2	546 503	61 64	0.32 0.31	29	58 58	3,340 3,100	37	— —	2.8 3.2	General condition poor, tempera- ture (37.0°—39.7° C). Amount of sputum ab. 100—200 ml. per day. — 19/1 47. Thoracostomia. Incisio et canalisatio. Exitus 24/2 46.
68	1766/II.46 ♂	26	Bronchiectasiae pulm. l.dx.	27/9.	46	7.1	569	66	0.40	43	79	4,790	30	—	14.2	General condition fair.
69	Thor. Dept. 756	♂	23	Abscessus l.dx.	18/6. 23/7.	45 45	6.3 6.2	542 544	52 62	30 34	60 70	3,310 4,020	37 35	— —	1.7 27.1	General condition impaired. Tem- perature varies from 37.0° to 39.0° C. Amount of sputum ab. 50—800 ml. per day. — 18/6 45. Thoracostomia. Incisio et ca- nalisatio.
70	Thor. Dept. 773	♂	38	Abscessus pulm. l.dx. Gangraena l.dx. Myodegeneratio et insuff. cordis.	16/8. 29/8. 4/9.	45 45 45	5.7 5.5 5.0	462 448 436	48 48 47	27 27 20	57 54 52	3,360 3,210 2,950	26 42	— — —	2.0 2.2 5.9	General condition very poor, loss of weight. Fever ad. 38.7° C. Exitus 4/9 45.
71	428/II.46 ♂	41	Abscessus pulm. l.dx.	16/2. 2/3. 8/3. 19/3. 28/3.	46 46 46 46 46	6.7 5.7 5.9 6.4 6.7	561 559 546 574 589	55 52 45 48 54	0.40 0.38 0.29 0.25 0.34	36 33 31 31 34	70 62 56 54 59	3,920 3,640 2,970 3,230 3,300	30	— — — — —	13.8 20.5 3.6 7.6 7.7	General condition markedly im- paired. Intermittent fever. Amount of sputum ab. 100— 400 ml. per day. — 8/3 45. Allo- plastia. — 18/3 46. Thoracosto- mia. Incisio et canalisatio. Exitus 6/7 46.
72	524/II.46 ♂	31	Abscessus pulm. l. sin.	2/3. 11/3. 19/3.	46 46 46	6.7 6.2 6.4	566 587 587	56 59 61	0.42 0.23 0.24	33 57 64	52 57 64	2,850 3,420 3,550	35	— — —	18.3 6.2 16.5	General condition impaired. Amount of sputum ab. 70—200 ml. per day. — 8/3 46. Incisio.
73	26/II.47 ♂	28	Abscessus pulm. l.dx.	17/11. 16/12.	46 46	7.8 7.3	572 615	59 58	0.17 0.32	32 31	52 54	3,340 3,350	—	— —	—	General condition impaired. Low fever.
74	2151/II.46 ♂	64	Abscessus pulm. l.dx.	28/11. 7/12. 9/12.	46 46 46	6.7 5.6 6.1	580 580 586	64 63 63	0.10 0.24	—	—	—	—	— — —	—	General condition impaired. Low fever. Amount of sputum varies from 30 to 250 ml. per day.

TABLE 6 (Continued)

No.	Case record	Sex	Age	Diagnosis	Date of test	Protein %	Chlorides mg %	Alkali reserve vol. %	Vitamin C mg %	Haematocrite	Haemoglobin	Erythrocytes	Non-protein nitrogen mg %	Urine		Remarks
														NaCl	Alb. % ₀₀	
75	2131/II.46	♂	52	Abscessus l.sin. pulm.	23/11. 46	7.4	579	69	0.11	31	58	3,480		—	20.6	General condition fair. Amount of sputum ab. 50—150 ml. per day.
76	41/II.47	♂	35	Abscessus pulm.l.dx. l.sin.	11/12. 46	6.8	618	64	0.20	28	50	2,310		—	19.5	General condition fair.
77	Thor. Dept. 788	♂	38	Abscessus pulm. Corpus al. pulm.l. sin.	14/12. 46	7.0	602	58	0.16	39	68			—	3.1	General condition good.
78	272/II.46	♂	64	Carcinoma pulm. l.dx.	16/2. 46	7.3	565	54	0.48	33	63	3,670	25	—	14.5	General condition fair.
79	16/II.47	♂	54	Carcinoma pulm. l.dx. cum metastat. costar. II—V l.dx. Empyema pleurae l.dx.	19/10. 46 12/12. 46	6.4 7.0	574 600	50 53	0.16 0.23	27 30	48 52	2,720 2,720		— —	10.4 7.9	General condition poor. Slight rise of temperature. — 29/10 46. Resectio costae et thoracostomia. Exitus 20/2 47.
80	31/II.47	♂	49	Carcinoma pulm. l.dx.	28/11. 46	7.1	653	52	0.10	37	65	3,850		—	31.7	General condition fair.
81	879/II.46	♂	38	Tub. pulm. cavernosa l.sin.	16/5. 46 18/5. 46 29/5. 46 18/6. 46	7.7 6.4 7.0 8.4	495 563 584 602	58 60 51 61	0.16 0.14 0.15	33 29 24 29	60 54 54 65	3,400 3,080 3,000		— — — —	5.1 23.2 9.4	General condition impaired. Patient feverish. — 7/5 46. Thoracostomia. Incisio et canalisatio.

82	1360/II.46	♂	51	Tub. pulm. caver- nosa l.sin.	16/8. 46 23/8. 46 31/8. 46 6/9. 46 10/9. 46 13/9. 46	5.5 5.3 5.0 6.0 6.0 4.6	576 540 557 564 557 550	58 55 58 55 52 50	0.22 0.19 0.17 0.16 0.14	29 29 27	31 29 57 55	59 60 60 60	3.820 3.650	27 44	— — — — — —	General condition poor, rise of temperature. — 17/7 46. Thoracostomia. Incisio et canalisatio. Exitus 16/9 46.
83	1661/II.45	♀	27	Empyema ac. pleu- rae metapneumoni- cum l.dx.	25/9. 45 10/10. 45	7.0 7.9	526 569	63 66	0.17 0.38	24	48	2.860	— —	— —	1.8	General condition impaired. — 21/9 45. Resectio costae et thoracostomia.
84	1123/II.45	♀	17	Empyema ac. anae- robicum pleurae l. dx.	12/7. 45 27/7. 45	6.5 6.1	478 506	52 55	0.37 0.39	29 33	59 64	3.300 3.420	33 32	— —	0.8 1.6	General condition poor. — 25/6 45. Resectio costae et thoracostomia. — Acc. Colitis ulcerosa. Perforatio sigmae. Peritonitis purulenta circumscripta pelvis minoris. Exitus 3/8 45.
85	76/II.46	♀	34	Empyema ac. pleu- rae l.dx. (Abscessus pulmonis l.dx.)	18/1. 46 1/2. 46	7.1 6.9	539 532	57 58	0.40 0.37	35	60 69	3.340 3.860	37 40	— —	10.8 4.7	General condition poor. — 28/12 45. Resectio costae et thoracostomia. — Acc. abscessus numeralia cerebri. Exitus 28/2 46.
86	1699/II.45	♂	33	Empyema ac. pleu- rae l.sin.	29/9. 45 9/10. 45	5.7 5.7	532 543	57 66	0.29 0.31	28 26	57 50	— —	35	— —	3.8 9.7	General condition impaired, tem- perature. — 24/9 45. Resectio costae et thoracostomia.
87	262/II.46	♂	30	Empyema ac. pleu- rae l.dx. Lues cerebrospinal.	25/1. 46 4/2. 46 19/2. 46 26/2. 46	5.5 6.8 5.7 5.3	539 539 585 577	48 54 58 65	0.26 0.29 0.28 0.25	24 34 21 34	50 53 50 60	2.750 3.170 3.600	— — — —	— — — —	0.7 2.36 20.4 22.6	General condition markedly poor. Temperature. — 22/1 46. Resec- tio costae et thoracostomia.
88	1022/II.46	♂	17	Empyema ac. pleu- rae tuberculosum l.dx.	21/5. 46 23/5. 46 3/6. 46	6.4 6.5 7.0	543 572 546	50 53 60	0.20 0.18 0.18	25 27 27	45 56 67	3.190 3.680 3.700	— — —	— — —	3.9 6.7	General condition markedly im- paired. Temperature varying betw. 37.0°—40.1°C.
89	52/II.47	♂	23	Empyema ac. pleu- rae l.sin.	18/12. 46	6.1	577	61	0.06	33	60	3.430	—	—	8.4	General condition poor, tempera- ture varying betw. 37.2°—40.0° C.

reduction in the alkali reserve within normal limits. On the other hand, when suppuration grew less and the general condition showed improvement the alkali reserve level began to rise. Before death the examined cases displayed a distinct reduction in the alkali reserve or a shift in the acid base balance of the organism towards acidity («premorttal acidosis»).

The decrease of the alkali reserve in chronic cases of pleural empyema is primarily attributable, in my view, to the severe infection and the abundant wound secretion, causing an accumulation of acid substances in the blood. The intoxication and the anoxia brought about by the severe infection seem to act as contributory factors in promoting acidosis. The rise in temperature concurrent with the suppuration appeared to have a reducing effect upon the alkali reserve. In chronic cases of pleural empyema accompanied by tuberculosis the alkali reserve values obtained did not diverge from those noted in non-specific cases of empyema. In amyloid cases no noteworthy differences could be traced compared with other equally severe suppurative conditions.

VII

THE BLOOD SUGAR

EARLIER INVESTIGATIONS ON BLOOD SUGAR IN INFECTIOUS DISEASES

Though it was recognized long ago that acute severe infections which occur in connection with diabetes aggravate the disease materially, often producing coma or changing latent diabetes to a manifest condition, there have also been reverse findings pointing to an improvement of diabetes during the period when the patient contracts some acute infection (LICHTWITZ 1927). The co-existent glycosuria may even disappear. CRECELIUS (1929) noted severe hypoglycemia in a diabetic who had developed appendicitis with accompanying peritonitis. Of the numerous other investigations of diabetic patients with surgical diseases I mention those of STRÖMBECK (1939).

Acidosis was earlier supposed to have a special importance in causing disturbance of the carbohydrate metabolism. UNDERHILL (1916) showed that acidosis increased the blood sugar content of the organism. PETER and GYELIN (1917) reported an interesting finding concerning the relation between blood sugar and the alkali reserve, when a drug called epinephrin was injected into a diabetic patient and then into a healthy person. When the alkali reserve was reduced, the blood simultaneously showed an excess of glycogen. The two investigators attributed the decline in alkality to the hyperglycemia which was produced.

The reduction of the carbohydrate tolerance in infectious diseases is an established fact, but opinions differ regarding the reason for this disturbance. ROHDENBURG and POHLMAN (1920), in *animal experiments*, noted hyperglycemia in connection with infections. They regarded the condition as an immunization against bacteria, an index of the degree of immunization. HIRSCH (1921) pointed out specifically that in experimental infections the increase of the hyperglycemia depends on the reduction in the alkali reserve, i.e. acidosis. SWEENEY (1928), in his experiments, injected diphtherial toxin into dogs. His findings seem to show that the hyperglycemia occurring in infections is primarily attributable to the derangement caused by toxins in the organs regulating sugar metabolism. FETZER (1932) made

corresponding tests on rats with a staphylococcal infection. The results of his detailed investigations seemed to indicate that the staphylococcal toxin causes disturbance in the storage of glycogen. SASKIN and MIRSKY (1935) report similar findings obtained in experiments on dogs.

In *clinical investigations* PEMBERTON (1920) and FLETCHER (1922) noted in cases of chronic arthritis both a normal blood sugar reaction and — not uncommonly — alimentary hyperglycemia. They attributed this to a diabetogenous disorder produced by the infection, with a reduction in carbohydrate tolerance. Glycosuria was rarely present in their cases. SEITZ (1922), among others, studied sugar metabolism in patients suffering from tuberculosis, salpingitis and ulcer ventriculi and in diseases of the gall-bladder. In tuberculous patients he found alimentary hyperglycemia of nearly the same severity as in staphylococcosis. Disturbances in the vegetative nervous system seemed to be especially significant in producing hyperglycemia in cases of gastric ulcer and diseases of the gall bladder. HOLSTI's (1924 and 1926) earlier investigations in cases of rheumatic arthritis confirmed the findings of PEMBERTON and FLETCHER. Later he made similar studies in other infectious diseases such as pneumonia, bronchitis, angina tonsillaris and cases of nephrosis. Besides normal blood sugar reactions subnormal blood sugar curves and alimentary hyperglycemia were noted. The activity of the disease did not seem to raise the blood sugar level. A subnormal reaction of the blood sugar, on the other hand, was frequent when the patient was recovering. According to HOLSTI the disordered carbohydrate metabolism was primarily due to changes in the function of endocrine glands caused by the infection. BERG (1924 and 1932), likewise, in his earlier investigation, was unable to establish any causality between the activity of the disease and the elevated blood sugar. In his later study he determined the blood sugar every hour from 8 to 20 o'clock while the patient was on an ordinary «sanatorium diet». The daily readings were normal only in four out of 16 cases. In the rest of the cases even marked hyperglycemia depending upon the severity of the disease was noted.

MACLEAN and SULLIVAN (1929) established a reduced carbohydrate tolerance in cases of encephalitis, tuberculosis, meningitis and morbilli. WILLIAMS and DICK (1932), after studying acute infectious diseases, report glycosuria in 41 per cent of their cases. It was most common in connection with influenza. These authors attribute the decline in the carbohydrate tolerance to the damage caused by the infection to the Langerhans' islands, which leads to lessened insulin formation.

ANDERSEN and SCHMIDT (1927) performed examinations in over 300 cases of different infectious diseases (malaria, exanthematous typhoid, morbilli, erysipelas, scarlatina, dysentery etc.). In spite of often considerable hyperglycemia glycosuria was not always present. Thus, the fasting level of blood sugar obtained by HAGEDORN's method was in a scarlatina patient 0.3 per cent without any sugar being traced in the urine. They explained this as due to the disturbance caused in the organism by toxins

In a case of septicaemia LAWRENCE and McCANCE (1931) referred the decline in carbohydrate tolerance to hypersecretion in the thyroid and suprarenal glands. RABINOWITCH (1932), on the other hand, suggested that due to infection a special enzyme destroying insulin was formed. He made blood sugar tests in diabetics both during febrile and feverless infection and found that it is not the fever but the infection that causes the decline in the carbohydrate tolerance. The same fact was emphasized by BREMS (1932), who carried out examinations in 77 diphtheria patients. In 14 severe or fairly severe cases out of this material the fasting level of the blood sugar exceeded 110 mg. per 100 cc. Several of the patients also displayed glucosuria. The blood sugar curve showed in the corresponding cases high maximum values and considerably protracted hyperglycemia often resembling diabetes. Glycosuria was then of almost constant occurrence.

PETRUNKIN (1935) studied the blood sugar tolerance in children. He determined the blood sugar level of 100 children in all with various infectious diseases, such as scarlatina, diphtheria, morbilli, pneumonia, purulent otitis and pseudocroup. In the beginning of the disease in scarlatina, diphtheria and morbilli the blood sugar curve rose sharply and did not return to the fasting level within 3 hours. Similar readings occurred in horses immunized with diphtheria toxins. In pneumonia, influenza and pseudocroup the blood sugar curves were low from the onset of the disease. On the basis of his own results and those of earlier investigators PETRUNKIN concluded that in diseases in which immunity can be acquired the system mobilizing blood sugar is in a state of hyperfunction when the disease first sets in and that there is some relation between the changes in the blood sugar level and the development of the immunity.

Of the numerous other investigators who have noted reduced carbohydrate tolerance in connection with infectious diseases, I mention SICK (1931), BREMS and NISSEN (1932), ROOT (1934) and HÜSCH (1936).

As is seen from the foregoing, investigations on sugar metabolism have also been carried out in chronic infectious diseases. Yet there seems to be no mention in the literature at my disposal of corresponding studies in cases of chronic empyema of the pleura.

Summarizing previous records in the literature we not uncommonly find a reduced carbohydrate tolerance both in acute and chronic infectious conditions. Besides normal blood sugar reactions alimentary hyperglycemia and simultaneous glycosuria are noted. In some acute infectious diseases, in addition, the fasting level may show a rise. According to MARBLE (1946) the decline in the carbohydrate tolerance due to infection might be attributed, theoretically, to one of the following four causes: 1) lessened production of endogenous insulin; 2) increased secretion of hormonal antagonists; 3) destruction of insulin; 4) interference with the storage of glycogen.

The normal blood sugar curve. Several investigators have determined the range within the limits of which the blood sugar curve varies in so-called normal cases on the basis of their carbohydrate tolerance tests,

comparing their readings with curves obtained in health. MALMROS (1928) showed that in healthy individuals the fasting value of blood sugar does not rise above 110 mg. per 100 cc., the maximum of the curve does not exceed 200 mg. per 100 cc. and that within two hours the sugar content is restored to 110 mg. per 100 cc. or less. With this behaviour of the blood sugar curve diabetes is out of question. He made the determinations by BANG'S (1913) method. HJÄRNE (1927) recorded similar readings in an earlier study. He found that the maximum was usually reached after about 20—40 minutes. SOISALO (1930), using HAGEDORN'S (1921) method, arrived in his extensive investigation at approximately the same results, as did HÜSCH (1936) and LUFT (1946). SOISALO regarded the fall in the blood sugar to 110 mg. per 100 cc. before two hours and a half as still normal. The fasting value was restored within 2 hours in 92 cases out of the 100 cases examined by him. In 8 cases the time required was over 2 hours, and in 5 out of these it was less than 2 ½ hours. According to SOISALO, the sugar curve had returned to the 'Nüchtern' level when it had fallen below 120 mg. per 100 cc. The maximum value usually occurred from 25 to 35 min. after the intake of glucose. Only in one case more than one hour passed, and it was then probably a case of convalescence.

Normally the blood sugar amount rises after the meal but it never exceeds 150 mg. per 100 cc. The sugar content is again normal after two hours (BEAUMONT and DODDS 1944). HIMSWORTH (1935) showed that the readings of the dextrose tolerance test varied with alterations in the patient's diet during the preceding week. When the food was poor in carbohydrate but rich in fats a diabetic curve could be obtained in healthy individuals.

FRASER (1941) and his associates found that if the patient was given 300 g. of carbohydrate for three days before the test the blood sugar rose sharply, in some cases to above 180 mg. per 100 cc., but was back to normal within the two hours. This is the so-called «lag» curve, showing an incapacity of the sugar storage mechanism to keep pace with the dextrose absorption, due to which there is a storage lag indicated by the rapid rise above the upper normal limit.

OWN INVESTIGATIONS ON BLOOD SUGAR IN CASES OF CHRONIC EMPYEMA OF THE PLEURA

I made examinations on 23 patients in all, who were among the severest suppurative cases in my material. In addition to determining the fasting level of the blood sugar, a blood tolerance test was performed in each case. The tests were made in the morning, by which time the patients had fasted about 12 hours. The dextrose tolerance test was made by administering to the patient 1 g. of glucose per kilogram of body weight in a 10 per cent

water solution. This glucose solution was consumed as fast as possible, in about 1—3 minutes. The blood sugar determinations were then made within 2 hours, the specimens being obtained at 10 minute intervals during the first hour and during the second hour at 15 minute intervals. The patients were weighed every morning prior to the tests.

After operations even considerable hyperglycemia could occur. Some authors attribute this to post-operative acidosis (CHASSIN and SCHAPIRO 1928 et al.). Others again find it due to hormonal disturbances which in connection with metabolic processes obstruct oxidation (THORESEN 1932; ROSCHER 1933 et al.). In view of this no blood sugar tests were undertaken in my cases immediately following operations.

Prior to the dextrose tolerance test the alkali reserve of the patients was determined in order to throw light upon the relation between possible acidosis and the changed blood sugar reaction.

The results of my investigations are shown in Table 7. When comparing the blood sugar curves obtained in cases of chronic empyema of the pleura with the normal values stated in the literature we note only few divergences. The *fasting values*, which ranged between 91 mg. per 100 cc. and 111 mg. per 100 cc. (average 99 mg. per 100 cc.) showed no marked divergencies. They were also in good accord with my blood sugar values in 8 normal cases, where the limit values were 89 mg. per 100 cc. and 102 mg. per 100 cc. (average 96 mg. per 100 cc.)

After the ingestion of glucose the *maximum* of the curve, which rose in two cases (Nos. 14 and 20), was 205 mg. per 100 cc. and 238 mg. per 100 cc. Yet glucosuria was present only in one (No. 14). The apex was reached in 5 cases after an hour or later (Cases 3, 7, 14, 20 and 41) and in 6 cases after 50 minutes. In the rest of the cases the maximum occurred after 30—40 minutes. When comparing these readings with the normal values recorded by SOISALO we note that in the 5 cases where the maximum occurred after one hour or later had an evident tendency to reduced dextrose tolerance.

The blood sugar curve *fell* below 120 mg. per 100 cc. within 2 hours in 18 cases, and in 5 (Cases 3, 9, 14, 17 and 20) the sugar content was still higher. In 92 of SOISALO's 100 normal cases the

TABLE 7
BLOOD SUGAR IN CHRONIC EMPYEMA OF THE PLEURA

No.	Sex	Date of examination	B l o o d s u g a r (mg %)											Sugar in urine (Nyl.)	Alk. res. vol. %		
			Fast- ing value	Time in minutes after the intake of glucose (1 g. per kg. of body weight, in 10 % water solution, per os)													
				10	20	30	40	50	60	75	90	105	120				
1	♂	22/3. 46	106	122	134	159	163	155	153	132	126	118	106	—	58		
2	♂	22/3. 46	110	121	145	153	186	172	172	162	147	130	108	—	55		
3	♂	1/4. 46	100	104	119	127	149	160	172	161	150	145	127	—	53		
6	♂	5/4. 46	91	96	112	116	120	116	110	106	100	98	91	—	62		
7	♀	15/4. 46	98	117	142	148	156	160	164	152	137	113	98	—	47		
8	♂	3/4. 46	94	125	133	160	172	172	153	147	141	116	100	—	59		
9	♂	10/4. 46	105	111	123	142	154	170	168	162	146	133	121	—	58		
10	♂	8/4. 46	100	119	144	156	152	144	137	133	127	121	107	—	60		
12	♂	21/5. 46	97	118	135	149	155	139	128	122	104	102	95	—	58		
13	♂	8/4. 46	100	121	133	148	161	144	137	131	127	121	117	—	63		
14	♂	20/4. 46	94	123	144	158	179	181	199	205	199	179	158	+	65		
15	♂	29/3. 46	93	100	117	121	129	139	135	121	106	100	93	—	56		
17	♂	29/3. 46	98	123	145	156	158	154	146	135	129	127	123	—	48		
18	♂	1/4. 46	98	117	125	141	166	139	135	129	125	119	115	—	52		
19	♂	19/9. 46	98	108	125	161	168	172	166	157	135	116	104	—	63		
20	♂	12/6. 46	102	108	116	155	184	202	238			176	162	—	56		
29	♂	9/4. 46	111	119	144	169	177	171	161	150	138	119	110	—	49		
31	♂	3/4. 46	98	118	141	153	141	125	116	106	98	96	96	—	54		
37	♂	21/3. 46	95	110	133	141	140	147	129	112	102	97	96	—	62		
39	♂	5/4. 46	96	104	127	145	155	166	153	116	102	94	92	—	55		
41	♂	21/3. 46	97	107	143	157	159	161	164	147	125	122	117	—	62		
45	♂	30/3. 46	98	114	128	147	131	124	108	104	99	98	98	—	62		
56	♂	21/2. 46	103	106	114	125	145	154	139	129	121	112	112	—			

fasting value was restored within 2 hours. When comparing these figures, proportionately, and taking into account the investigations of HJÄRNE, MALMROS and HÜSCH, the 5 cases mentioned seem to exhibit an evident tendency to a lowering of the carbohydrate tolerance.

It is remarkable that in Case 20 no glucosuria was present in spite of the considerable alimentary hyperglycemia. Glycosuria occurred, on the other hand, in Case 14 where the hyperglycemia is less severe. The urinary sugar had not been determined in this case. It is possible that in Case 20 the lack of glycosuria was due to a transitory disturbance in the organs regulating sugar metabolism, which was

caused by toxins. This theory is supported, for instance, by SWEENEY's (1928) experiments on rabbits, into which he injected diphtheria toxin.

In four tuberculous empyema cases (12, 18, 19 and 56) the blood sugar reactions were normal. There was no fever in my cases during the investigations.

There seems to be no interrelation between the blood sugar level and the alkali reserve in my cases.

Discussion of Results

On the basis of the foregoing we can say that besides normal blood sugar curves in some cases of chronic empyema of the pleura there were in others changes pointing to a reduction of the carbohydrate tolerance. My readings are thus in keeping with those recorded in the literature on the basis of investigations made in various acute and chronic infectious diseases. The decline in carbohydrate tolerance noted in the cases of chronic empyema of the pleura examined is less marked than in several acute infections reported in the literature. The number of cases studied is possibly too small to justify definitely reliable conclusions, but yet even these seem to shed some light on the carbohydrate metabolism in cases of chronic pleural empyema.

All the patients examined by me were under treatment at the same hospital and thus were on a similar hospital diet which due to war-time conditions was deficient in some elements, especially in fats. This justifies us in excluding the possibility that the diet might have affected the changes in blood sugar in those of my cases which show a reduced dextrose tolerance.

In the cases recorded the decline in carbohydrate tolerance is evidently due to infection. It is not improbable that the severe chronic infection may cause disturbances in the Langerhans' islands, which would lead to an obstruction of the insulin production. The slight latent diabetes produced in this manner would become manifest in the dextrose tolerance test.

Summary

In chronic cases of empyema of the pleura, after the ingestion of glucose, the blood sugar curve showed in some cases changes pointing

to a reduction of the carbohydrate tolerance. In two of the 23 cases examined the maximum of the curve exceeded 200 mg. per 100 cc., in 5 cases the apex was reached after one hour or later and in 5 cases the fasting level was not restored within two hours. Glycosuria was present in one case. The fasting values were normal. In four tuberculous empyema cases the blood sugar reactions were normal. The reduction in the carbohydrate tolerance, in my opinion, is primarily attributable to the disturbance in the organs regulating sugar metabolism, which is due to the intoxication caused by the severe chronic infection.

The readings are thus in agreement with results recorded in literature of investigations performed in various other both acute and chronic infections. The fall in carbohydrate tolerance was in the cases of chronic empyema of the pleura less conspicuous than in several acute infections described in the literature.

VIII

VITAMIN C

ON THE VITAMIN C CONTENT OF BLOOD

In spite of numerous experimental and clinical investigations the physiology of vitamin C and its importance for cell life have not yet been explained satisfactorily. There is no doubt about the fact that it plays a rôle of some significance in the biological process of oxidation and especially in the production of collagen in mesenchymal tissue.

In examining the vitamin C concentration of the organism two different chemical methods have been used. The vitamin C level is either determined from the blood, or a fixed amount of ascorbic acid is administered, and the vitamin C amount excreted in the urine is gauged by means of the so-called balance curve.

Several investigators agree that the vitamin C content varies considerably in healthy individuals. There are consequently different opinions as to what concentration should be regarded as «normal» or «lowered.» The diversity of the findings recorded in the literature is mainly due to diet, alternation of seasons, and the different techniques employed in determining vitamin C.

A remarkably great number of investigations have been carried out to establish the «normal» level of ascorbin acid in the blood and the lowest level below which values are indicative of less or greater deficiency of vitamin C. The literature on this subject is at present so extensive that only a few from among the authors representing a variety of opinions will be mentioned here. Thus WESTERGAARD (1937) found by means of a modification of FARMER and ABT's (1935) method that the plasma ascorbic acid content of 31 nurses varied between 0—1 mg. per 100 cc., the average being 0.28 mg. per 100 cc. DAGULF (1939) made similar determinations by the techniques of LUND and LIECK (1937) and FARMER and ABT. According to the former method the average was 0.242 mg. per 100 cc., by the latter the values were somewhat higher. A few subjects also showed a total absence of vitamin C although no symptoms pointing to scurvy had appeared. NILSSON (1939) obtained zero values by LUND and LIECK's method in 9 out of 21 healthy individuals. Using a modification of this technique DIRS

(1940) noted in the serum of 66 healthy subjects values which varied from 0.02 to 1.15 mg. per 100 cc. Numerous other investigators (H. WORTIS, LEIBMANN and E. WORTIS 1938; HERLITZ 1938; ODIN 1939; KIVIMÄKI 1940; TRIER and PEDERSEN 1941; SIMOLA 1941; PITKÄNEN 1944 et al.), showed that there was no hard and fast line between normal and pathological vitamin C values. ODIN, for instance, regarded as hypovitaminosis only cases exhibiting definite symptoms of disease. SIMOLA demonstrated in Finland, in war-time conditions, markedly low serum vitamin C values without any symptoms indicative of hypovitaminosis being present. PITKÄNEN examined 72 healthy individuals. The limit values for vitamin C were in these 0.30 and 1.60 mg. per 100 cc., the average being 0.57 mg. per 100 cc. He used in his investigations a modification of FARMER and ABT's technique.

In the relatively extensive investigations on the vitamin C concentration of blood carried out at the University Department of Medical Chemistry, Helsinki, the dichlorophenolindophenol technique described earlier was used. The variations generally followed changes of seasons. The average of the results collected over several years showed the vitamin C content of the serum to be 0.70 mg. per 100 cc. in the autumn and 0.41 mg. per 100 cc. in the spring. Of the investigations carried out in war time it should be mentioned that the vitamin C concentration of a certain number of doctors varied in the spring of 1941 between 0.38 and 0.60 mg. per 100 cc. (average 0.48 mg. per 100 cc.). The corresponding values for university students ranged from 0.48 to 0.73 mg. per 100 cc. and those for soldiers from 0.13 to 1.60 mg. per 100 cc. (average 0.48 mg. per 100 cc.). In the spring of 1942 the values fluctuated for soldiers between 0.19 and 0.54 mg. per 100 cc. (average 0.36 mg. per 100 cc.), for labour conscripts from 0.14 to 1.03 mg. per 100 cc. (average 0.35 mg. per cent) and for civilians from 0.12 to 1.37 mg. per 100 cc. (average 0.51 mg. per 100 cc.). In January and February, 1943, two and a half years after the outbreak of the war, the vitamin C concentration varied in advanced medical students from 0.11 to 1.75 mg. per 100 cc. (average 0.49 mg. per 100 cc.). The high values exceeding 1 mg. per 100 cc. were in most cases due to the patients having taken vitamin C preparations or to a diet rich in vitamin C.

SURVEY OF EARLIER INVESTIGATIONS ON CHANGES IN THE VITAMIN C CONTENT OF SURUM IN INFECTIOUS DISEASES

Several investigators emphasize the importance of vitamin C especially in combating infection, in connection with the so-called antigen — antibody reaction. It seems to have a favourable effect both upon immunization and non-specific resistance, the increase of the bactericidal capacity of blood. JUSATZ (1939), among other authors, attributes the decline in vitamin C concentration which occurs in infectious diseases to this fact, not e.g. to fever. Yet opinions differ on this point. SIMOLA and BRUNIUS (1933)

were not able to show that hypovitaminosis should in any way impair immunization. WEGEMER and BÜSING (1942), likewise, who made examinations on tuberculous patients, were unable to establish any connection between the ascorbic acid level and the bactericides of blood. Vitamin C of course is not a chemotherapeutic agent such as the sulphonamides, but it has an indirect effect in strengthening the organic cells and the mesenchymal tissue which participate in the warding off of infection.

A great number of authors have been able to show that in acute and chronic infectious diseases the need of the organism for vitamin C increases. Especially in febrile *acute infectious diseases* such as pneumonia, diphtheria, scarlatina, typhus, acute arthritis and influenza the vitamin C level can be lowered markedly (SCHROEDER 1935; GREENWALD and HARDE 1935; RINEHART, GREENBERG and CHRISTIE 1935; DIECKHOFF and SCHÜLER 1938; LEPPÖ 1939 et al.). Several authors have noted correlation between the height of the temperature and the vitamin C level. The higher the fever the less is the excretion of vitamin C in the urine. A corresponding decrease in the vitamin C content of blood occurs depending upon the height of the temperature. The deficiency present in the organism, in these cases, cannot always be corrected even by abundant intravenous administration of vitamin C (HAUSBERGER and NEUERSCHWANDER-LEMMER 1939).

In various *acute surgical infections* several investigators have noted a secondary reduction of the vitamin C level. LAUBER, BERSIN and NAFZIGER (1937), in their experiments on rabbits, noted an evident decline of the vitamin C content of the blood in streptococcal infections, in peritonitis and in phlegmonous conditions, and also in clinical cases such as mastitis purulenta and osteomyelitis. They also report having observed in a severe infection a corresponding decrease in the urinary excretion of vitamin C. Several other authors have corroborated, in their investigations, the findings of the foregoing (FORSTER 1937; EITEL and TRUCK 1937; WACHSMUTH and HEINRICH 1938 et al.). TIITINEN (1944) obtained reduced vitamin C values of the serum in the cases of acute osteomyelitis examined in connection with his investigation on haematogene osteomyelitis.

Among *chronic diseases*, tuberculosis and osteomyelitis have been the object of especial investigations on vitamin C metabolism. In both these conditions reduced vitamin C values of the blood have been obtained. The reduction has been attributed to the increase in the rate at which the organism consumes vitamin C or to disturbances in resorption, and to the disproportion between the requirement of the organism for vitamin C and the amount of the vitamin actually taken in food.

TRÜCK (1938) records a reduced vitamin C level in two cases of suppurating chronic *osteomyelitis*. Four cases of acute suppurative osteomyelitis, on the other hand, showed normal vitamin C values. ABBASY, HARRIS and HILL (1937) found that in 17 active cases of osteomyelitis the urinary excretion of vitamin C had diminished, also during the tolerance test, which in their opinion pointed to increased consumption owing to the infection. Along with an improvement of the disease the urinary excretion of vita-

min C became normal. The most conspicuous reduction of the vitamin C level occurred in the active cases and a less marked lowering in those which had partly recovered.

LAUBER, BERSIN and NAFZIGER (1937) showed that the vitamin C reduction was much more marked in chronic diseases such as tuberculosis of the bone and the joints, than in acute infections. WIDENBAUER (1937) declared that the consumption of vitamin C in the organism was the larger the severer the infection. In his view the daily vitamin C requirement in chronic infections such as bone tuberculosis and rheumatism should be estimated on the basis of the clinical condition and the sedimentation rate. BARTLETT, JONES and RYAN (1940) established in various diseases such as osteomyelitis, gastric carcinoma and ulcerating colitis below 0.43 mg. per 100 cc. as the average vitamin C level of the blood plasma. The normal values ranged, according to them, between 0.8 and 1.2 mg. per 100 cc. After operation the vitamin C level of the blood was at its lowest, while the vitamin C content of the urine increased.

Of chronic diseases the vitamin C metabolism has been most frequently investigated in *pulmonary tuberculosis*. The results obtained by numerous investigators in saturation tests show that if ascorbic acid is administered to tuberculous patients, the urinary excretion of vitamin C is less in these patients than in healthy individuals (HASSELBACH 1936 and 1937; HORELLI 1937). Several authors have also noted that the vitamin C deficiency is due to the disease in question and is larger in advanced stages of pulmonary tuberculosis (MELZER 1938 et al.). The last-mentioned author consequently recommends, in mild cases, a diet rich in vitamin C, e.g. plenty of fruit, and in severe cases a daily intake of crystalline ascorbic acid.

Investigations on the vitamin C concentration have generally showed the level to be lower in cases of pulmonary tuberculosis than in healthy individuals. B. and E. GROTH-PETERSEN (1939) declared that »tuberculous patients usually require a larger amount of vitamin C than healthy persons in order to achieve an equal ascorbic acid concentration of the blood.» DAGULF (1939) found that the ascorbic acid level of the blood serum of tuberculous patients was markedly lower in different seasons than that of healthy individuals. The vitamin C level of tuberculous patients was in the spring 0.10 mg. per 100 cc. and in the autumn 0.48 mg. per 100 cc. The corresponding values for healthy individuals were 0.22 and 0.90 mg. per 100 cc.

RAUNIO (1941) in his study of the vitamin C content of the serum of tuberculous patients came to the conclusion that the patients who are on a »sanatorium diet» show, on an average, a lowering of the ascorbic acid content of the serum in the spring and early summer. In exudative cases of pulmonary tuberculosis the vitamin C deficiency is larger than in productive and exudative-productive types of the disease. In healthy persons and in mild cases of tuberculosis no noteworthy differences were observable in the vitamin C content of the serum. In April and May, 1939,

the average ascorbic acid content of 102 examined patients with pulmonary tuberculosis was 0.27 mg. per 100 cc. In the August and September of the same year the corresponding value was for 104 patients 0.58 mg. per 100 cc., and in June and July, 1940, in 32 patients 0.13 mg. per 100 cc.

Yet even diverging findings have been recorded. WOLF (1945) declares that patients with pulmonary tuberculosis exhibit in severe terminal stages a rise of the ascorbic acid level of the blood. He undertook examinations on 50 cases in all and obtained markedly high values (3.0 mg. per 100 cc.). No other investigators have recorded a vitamin C level of this height in corresponding cases.

The American ZERBINI (1945) noted in the investigations on the vitamin C content of the blood plasma which he carried out in connection with operations on chest organs a reduced vitamin C concentration in various chronic diseases of the lung and in cases of carcinoma of the oesophagus. 22 patients in all showed before operation an average plasma vitamin C level of 0.15 mg per 100 cc. The ascorbic acid amount was normal (1.8—1.2 mg. per 100 cc.) in only one case, and in 9 cases the plasma contained no vitamin C. After operation, while the wound was suppurating or an empyema was developing, the ascorbic acid level fell. In some cases of post-operative empyema, where the vitamin C amount was before operation 1.2 mg. per 100 cc., the ascorbic acid content of plasma was zero still 45 days after operation. By an abundant administration of vitamin C the amount of ascorbic acid in the plasma could generally be made to rise.

The possible share of vitamin C in cases of severe chronic wound suppuration, so-called «super-infection», when the wound is healing very slowly, has not yet been made clear. According to LÖHR (1937), hypovitaminosis is often present in these cases. He declares that wound diphtheria, for instance, occurs more often in the winter months, and that fresh wounds do not generally exhibit suppuration of this kind.

In contrast to the peace-time cases mentioned in the foregoing no equally extensive investigations have been undertaken in severe chronic cases of wound suppuration due to war injuries. In the literature I have only come across CONRAD'S (1944) study dealing with these diseases. He noted in 16 severe chronic cases of suppurating bullet wounds a reduction of the vitamin C content varying from 0.2 to 0.3 mg. per 100 cc. In five normal cases the corresponding values ranged from 0.36 to 0.44 mg. per 100 cc. The average was for the suppurating cases 0.23 and for the normal cases 0.40 mg per 100 cc. No clinical symptoms of hypovitaminosis occurred in any of the cases. Three of these patients had an empyema cavity, the ascorbic acid concentrations of the blood being 0.20, 0.24 and 0.27 mg. per 100 cc. respectively. He attributed the hypovitaminosis to the increased need of the organism for vitamin C, due to the increased metabolism caused by the infection.

OWN INVESTIGATIONS ON THE VITAMIN C CONTENT OF SERUM
IN CASES OF CHRONIC EMPYEMA OF THE PLEURA

When evaluating the vitamin C content of the serum in cases of chronic empyema of the pleura it should be remembered that the patients under clinical treatment were daily given from 75 to 150 mg. of vitamin C («Orion» ascorbin tablets à 0.025 g.) Only in 34 cases was the vitamin C concentration of the serum determined on admission to the hospital, and before vitamin C had been administered. The remaining 25 cases were under clinical treatment when the investigations were started and had thus received vitamin C. Serum vitamin C determinations were also carried out after operations. This enabled me to find out, more accurately, which of the changes that were noted in my cases in the vitamin C content were directly due to the operations.

The results of my investigations are shown, in Cases 1—21, in the graphic charts 16—20 and in Cases 22—59 in Table 5. When reviewing the data we find that considerable variations occurred in the vitamin C level of the serum in cases of chronic empyema of the pleura. In the following those 34 cases where the patients' vitamin C level was determined on admission to the hospital are treated as a separate group. Both these patients and the other 25 were given vitamin C regularly, every day.

In order to find out whether there was any hypovitaminosis in the suppurating cases of pleuritis, the findings obtained in normal cases and those representing cases of chronic pleural empyema can be classified into distinct groups. This makes it possible to estimate whether the values are lower in the empyema cases than in the control subjects. Though it may seem presumptuous to define the values, on the basis of this classification, as «lowered» or «normal», the division has some significance, if we can assume that when the blood serum contains a larger amount of this vitamin the vitamin C standard of the organism is better. However, it is difficult to establish a basis for classification in this instance, as can be seen from the greatly differing views put forward in the literature on the question of the vitamin C concentration of blood. Taking into account, primarily, the results of investigations reported in the literature which have been carried out by the same tech-

VITAMIN C CONTENT OF SERUM IN CASES OF CHRONIC EMPYEMA OF THE PLEURA
(CASES 1—21; FIGURES 16—20¹)

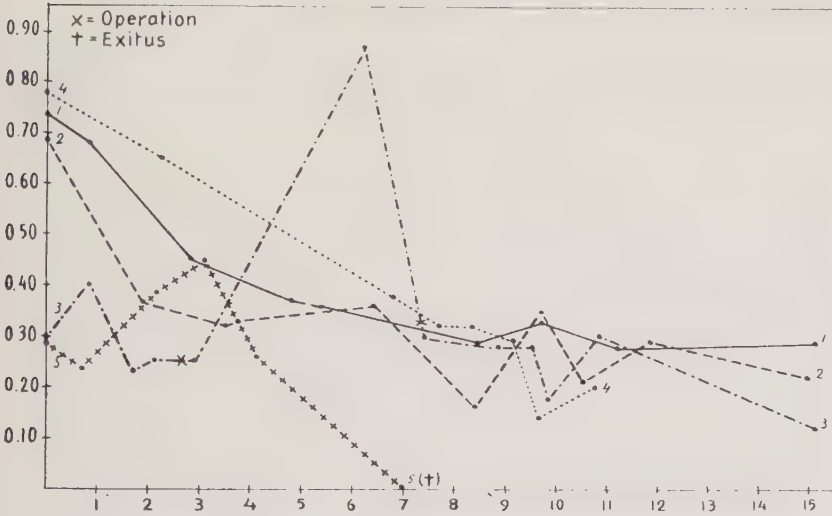


Fig. 16. — Cases 1—5. Ordinate: Vitamin C content of serum (m. per 100 cc.).
Abcissa: Time in months.

¹ The time when the first investigation in these cases was carried out was the same as that of the corresponding cases in Figs. 6—10.

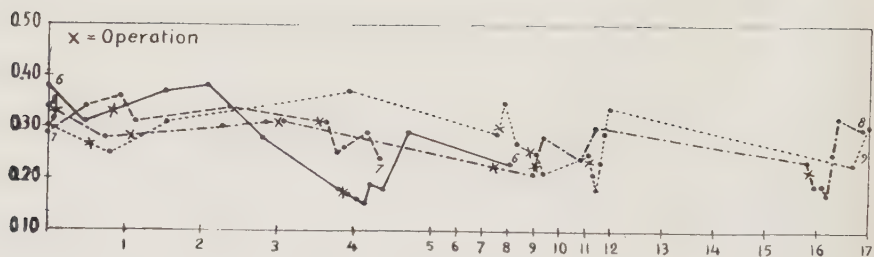


Fig. 17. — Cases 6—9. Ordinate: Vitamin C content of serum (mg. per 100 cc.).
Abscissa: Time in months.

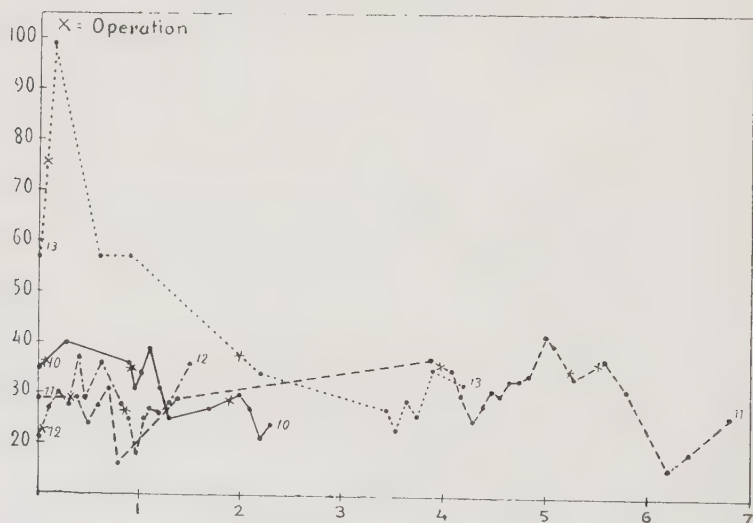


Fig. 18. — Cases 10—13. Ordinate: Vitamin C content of serum (mg. per 100 cc.).

Abscissa: Time in months.

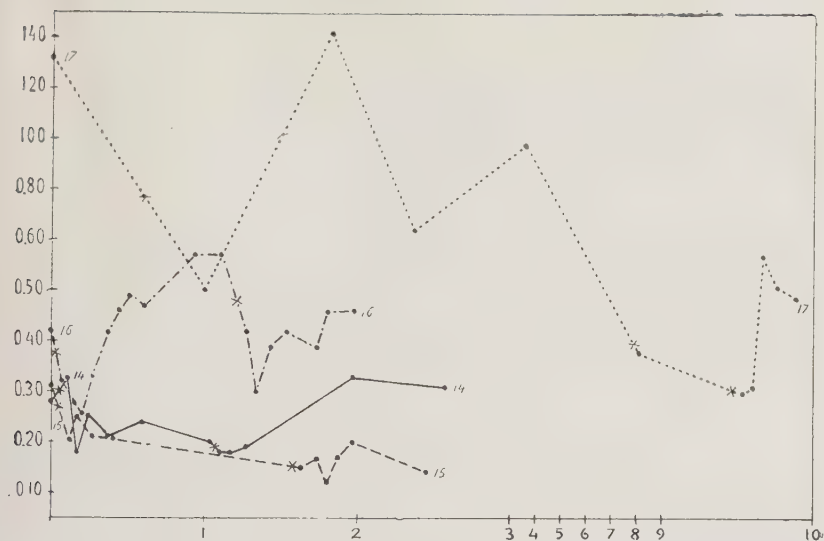


Fig. 19. — Cases 14—17. Ordinate: Vitamin C content of serum (mg. per cent 100 cc.).

Abscissa: Time in months.

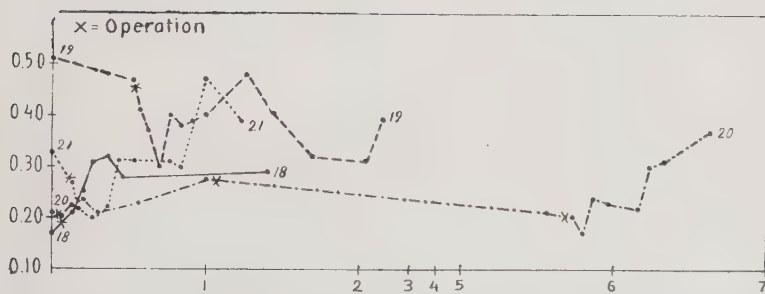


Fig. 20. — Cases 18—21. Ordinate: Vitamin C content of serum (mg. per 100 cc.).

Abscissa: Time in months.

nique that I have employed, I have chosen the classification used by PITKÄNEN, among others (1944):

Ascorbic acid of the serum below 0.40 mg. per 100 cc. less good									
»	»	»	»	»	0.40—0.60	»	»	»	» relatively good
»	»	»	»	»	above 0.60	»	»	»	» good

Table 8 is based on this classification. Those patients who had not been given vitamin C form a separate group and those who had received vitamin C during clinical treatment another. In the latter cases the first value directly independent of operations was taken into account.

According to the Table both groups contained a higher percentage of values under 0.40 mg. per 100 cc. in cases of chronic empyema than in the 20 control subjects. 43 empyema patients in all showed values below 0.40 mg. per 100 cc. A vitamin C concentration above 0.60 mg. per 100 cc. occurred in 9 cases with a chronic empyema, of whom 8 had taken ascorbic acid while under hospital treatment. In the 34 cases mentioned the lowest ascorbic acid content of the serum was 0.11 mg. per 100 cc. (Case 22), the highest 0.72 mg. per 100 cc. (Case 51). In most of these patients the fluctuations evidently followed the seasons. The lowest serum vitamin C values occurred, mainly, from March to June, and the highest from July to February. Among 25 patients who had received vitamin C, the lowest value shown was 0.20 mg. per 100 cc. (Cases 24 and 26) and the highest 1.3 mg. per 100 cc. (Case 17).

Table 9 presents the cases divided into two groups on the basis of the time of the year when the investigations were carried out. Among patients who did not receive vitamin C, in examinations made from March to June, 18 showed levels which were on an average lower than in 16 cases examined in July—February. In the former cases the vitamin C content of the serum was on an average 0.28 mg. per 100 cc. and the limit values 0.17 and 0.51 mg. per 100 cc. (Cases 18 and 35). The corresponding values for the latter group were 0.38, 0.11 and 0.72 mg. per 100 cc. (Cases 22 and 51). In the 25 cases who had been given vitamin C the vitamin C amounts were in the main larger than in those who had not received any vitamin C. The clinical condition of these patients varied considerably,

TABLE 8

VITAMIN C CONTENT OF SERUM IN CHRONIC EMPYEMA OF THE PLEURA AND IN CONTROL CASES ACCORDING TO THE HEIGHTS OF THE VALUES (MG %)

Group examined	Number	Patients who had not received vitamin C				Patients who had received vitamin C during treatment			
		below 0.40		0.40—0.60		below 0.40		0.40—0.60	
		Number	%	Number	%	Number	%	Number	%
Chronic empyema....	34	28	82	5	15				
Chronic empyema....	25					15	60	2	8
Control cases ¹	20	8	40	10	50				
				2	10			8	32

¹ In 10 of the control cases the determinations were made in the autumn and in the spring.

In the autumn the average was 0.45 mg. %, the lowest value 0.33 mg. % and the highest 0.57 mg. % (cf. Table 2).

In the spring the values were on an average 0.43 mg. %, the lowest 0.31 mg. % and the highest 0.82 mg. %.

TABLE 9

VARIATIONS OF THE VITAMIN C AMOUNT DEPENDING ON THE SEASON IN CHRONIC CASES OF EMPYEMA OF THE PLEURA AND IN CONTROL CASES (MG %)

Group examined	Number of cases		Average		Limit values	
	March—June	July—February	March—June	July—February	March—June	July—February
Chronic empyema ¹	18	16	0.28	0.38	0.17—0.51	0.11—0.72
Chronic empyema ²	12	13	0.50	0.44	0.20—1.30	0.26—0.78
Normal cases	10	10	0.43	0.45	0.31—0.82	0.33—0.57

¹ Cases in which the examinations were performed before the administration of vitamin C.

² Patients who had received vitamin C during treatment.

primarily owing to the suppuration of the wound which followed operation. Evidently due to this fact, values fluctuating within a wide range were also obtained in spite of the intake of vitamin C. From March to June the lowest value, among 12 cases, was 0.20 mg. per 100 cc. (Cases 24 and 26) and the highest 1.30 mg. per 100 cc. (Case 17), the average being 0.50 mg. per 100 cc. In the 13 cases examined in July-February the corresponding values were 0.26 (Case 42), 0.78 mg. per 100 cc. (Case 4), and the average 0.44 mg. per 100 cc. Compared with normal subjects the average level of the patients who had been given vitamin C is somewhat higher in March—June.

After operation a reduction of the vitamin C level of the serum was observable, as can be seen in Cases 6, 8—16, 18—21 (Fig. 17—20), and in Case 32 (Table 5). Of these 15 cases 13 showed a 0.1 mg. per 100 cc. average reduction of the serum vitamin C level. The limit values were 0.01 (Cases 20 and 32) and 0.18 mg. per 100 cc. (Case 13). The lowest value generally occurred on the 2nd—6th day after operation. Three patients had it on the 7th—8th post-operative day. In two out of these cases (Nos. 8 and 11) the wound secretion was relatively abundant, and one (Case 6) exhibited, in addition to the wound infection, a markedly impaired general condition. Two cases (Nos. 12 and 18), on the other hand, showed no post-

operative lowering of the vitamin C level of the serum. In these cases the pre-operative values were 0.21 and 0.17 mg. per 100 cc. The former patient had a rise of temperature during the examination in question, and in the latter case the operation was of a minor type. In both cases the wound suppuration was rather abundant. After operation the pre-operative value was restored even in severe infections within the first four weeks, when the patients were regularly given vitamin C, except in one case (No. 14). In Case 15 the value obtained before operation was not restored, evidently owing to the renewed operation. In cases 7, 17, 31, 33, 35, 38, 49, 50 and 51, with a suppurating operation wound, reduced vitamin C values, compared with other examinations, were noted, directly owing to operation.

In post-operative cases of prolonged suppuration even markedly varying vitamin C values of the serum could be noted. The limit values were in these cases 0 (Cases 5 and 24) and 1.44 mg. per 100 cc. (Case 41). In severe cases ending *fatally* the lowest serum vitamin C values in my examinations occurred at the terminal stage of the disease. Thus in Case 5 no vitamin C was found in the serum two days before death. About from 7 to 3 months earlier the values varied in 6 examinations between 0.24 and 0.45 mg. per 100 cc. In Case 24, likewise, no vitamin C was discovered in the serum 6 days prior to death. In two earlier examinations the values were 0.20 mg. per 100 cc. In Case 25, in two examinations, the ascorbin acid amount of the serum was 0.39 and 0.31 mg. per 100 cc. Ten days before death, in Case 26, the vitamin C level was 0.20 mg. per 100 cc. In Case 27 it was one day preceding death 0.19 mg. per 100 cc. In three earlier examinations the values varied from 0.23 to 0.30 mg. per 100 cc. Six days before death Case 28 had 0.27 mg. per 100 cc. of vitamin C in the serum. In four earlier examinations the level varied from 0.29 to 0.36 mg. per 100 cc. No clinical symptoms of avitaminosis were exhibited in these cases. All except Case 25 had a total cavity. In the last-mentioned case the cavity was comparatively small, but pericarditis was present as a complication.

In other post-operative cases of prolonged suppuration patients exhibited small seasonal variations, in spite of the regular intake of vitamin C. Thus in the severe Case 1, who owing to the removal of the lateral wall of the cavity had a very extensive suppurating surface, the values varied from 0.28 to 0.74 mg. per 100 cc. in 11

examinations made within about 15 months. In 6 examinations the vitamin C amount was below 0.40 per 100 cc. Before the last examination the patient had been at home on leave and had not taken ascorbic acid. At the time in question — October — the vitamin C amount of the serum was 0.29 mg. per 100 cc., and the suppurating surface was much smaller. Case 2 also had long-standing suppuration. This patient, in addition, suffered from tuberculosis. In 10 examinations during about 15 months the vitamin C values of the serum ranged between 0.21 and 0.69 mg. per 100 cc. A vitamin C amount below 0.40 mg. per 100 cc. occurred in 9 examinations. As in the case mentioned earlier, so also in this case the comparatively lowest values occurred in the spring. Patient No. 3 was another severe case, where the suppuration was at times profuse. During about 15 months, in 12 examinations, the vitamin C amount of the serum varied from 0.12 to 0.87 mg. per 100 cc., 10 examinations yielding a value below 0.40 mg. per 100 cc. The lowest value of this patient occurred in the autumn. In Case 4 the lowest value obtained in 8 examinations made within about 11 months was 0.19 mg. per 100 cc. and the highest 0.78 mg. per 100 cc. Six examinations showed a vitamin C concentration below 0.40 mg. per 100 cc. The lowest values occurred in the spring, when the patients, who were on home leave, did not take Vitamin C.

In other cases, also, where several operations had been carried out in order to eliminate the empyema cavity, reduced vitamin C values of the serum, directly independent of operations, could be noted in connection with prolonged suppuration. We find this to be the case in Cases 6, 8—15 and 18—20. Cases 35, 36, 42, 43, 45 and 51, likewise, showed values below 0.40 mg. per 100 cc., even after about 6 weeks (Case 35) to 3 ½ months after operation. Case 41, whose vitamin C concentration was in the last examination 0.19 mg. per 100 cc., had recently returned from home leave, and had not taken vitamin C. In 6 cases in all (Nos. 17, 33, 37, 40, 41 and 55) the level exceeded 1 mg. per 100 cc., the highest value being 1.44 mg. per 100 cc. (Case 41). All these patients received vitamin C while they were under clinical treatment.

Of the patients with *chronic bronchial fistula* Cases 22 and 23 did not receive vitamin C. In three examinations made on the former patient the level was below 0.40 mg. per 100 cc. (0.30, 0.26 and 0.11 mg. per 100 cc.) The lowest value occurred at an exami-

nation after the recent closing of the bronchial fistula while the suppuration still persisted. In Case 23 two examinations revealed reduced levels (0.24 and 0.27 mg. per 100 cc.). This patient exhibited a less abundant suppuration than the former. Case 54, who had developed tuberculosis as a complication, showed in the summer months values 0.27, 0.28 and 0.32 mg. per 100 cc.

No noteworthy differences were detected in *tuberculous* chronic cases of empyema compared with other cases. In 10 instances the limit values were 0.16 mg. per 100 cc. (Case 2) and 1.1 mg. per 100 cc. (Case 55). All of these patients exhibited lowered vitamin C values of the serum. Yet in one case (No. 19) values below 0.40 mg. per 100 cc. did not occur until after the operation carried out, while the wound was suppurating.

The vitamin C level of *febrile* patients, compared with other cases, was not any lower. In Case 5 the values obtained in 5 examinations undertaken within four months ranged from 0.24 to 0.45 mg. per 100 cc. Before death, when no vitamin C was detectable in the serum, the patient was feverless. In Case 25 the vitamin C concentration established during fever was 0.39 mg. per 100 cc. Both these patients, who were under clinical treatment, had taken ascorbic acid. Cases 10, 12, 20 and 29, instead, who had a temperature on admission to the hospital, had not received vitamin C before the first examination. The ascorbic acid concentrations of the serum were in these cases respectively 0.35, 0.21, 0.21 and 0.28 mg. per 100 cc. In Case 29 the corresponding value was about one week later 0.32 mg. per 100 cc. The temperature was then normal, but the purulent discharge from the total empyema cavity was abundant.

Comparative Material (Table 6)

Chronic diseases of the lung and cases of acute suppurative pleuritis show no conspicuous differences compared with chronic cases of empyema of the pleura. In 34 cases of the last-mentioned condition, where the examinations had been performed before the intake of vitamin C, the limit values were 0.11 and 0.72 per 100 cc. Values under 0.40 mg. per 100 cc. occurred in 28 cases (about 82 per cent). In 30 cases of the comparative material the limit values were 0.06 (Case 89) and 0.61 mg. per cent (Case 69). 25 out of these cases (about 83 per cent) had a vitamin C content of the serum below 40 mg. per 100 cc. Out of 9 patients with bronchiectasis 6

showed lowered values, and out of 9 cases of pulmonary abscess 8. Evident hypovitaminosis was present in two of three patients with carcinoma of the lung, likewise in two examined cases of pulmonary tuberculosis. Values below 0.40 mg. per 100 cc. were noted in each of the 7 acute cases of empyema of the pleura. The lowest vitamin C values of the serum occurred, evidently due to the severe infection, in cases with a rise in temperature and a poor general condition.

Discussion of Results

As we see from the foregoing, several patients with chronic empyema of the pleura exhibited a vitamin C level which was less good, and reduced in comparison with that of normal cases. It should, however, be noted, that owing to the method of investigation I employed my results may perhaps be slightly too high. In several cases the values were lower than the average level, 0.24 mg. per 100 cc., established by CONRAD (1944) in three cases of chronic empyema. The lowering of the vitamin C concentration of the serum which was entirely independent of the temperature was most marked, on an average, in the spring and early summer. In especially severe infections a decline of the vitamin C content of the serum or a total lack of the vitamin could be noted at the terminal stage of the disease. In spite of the intake of vitamin C lower vitamin C values, compared with normal cases, occurred in the most severe infections.

Since the patients received vitamin C while under treatment, a comparison with levels obtained in health seems to lack justification. In fact, lower values were noted after recovery, in many cases, than during the disease (cf. Table 5).

Primarily, the decline in the vitamin C concentration of the serum seems to be attributable to the severe chronic infection. The lowest values noted seem to indicate that the increased need for more vitamin C is mainly due to the increase in metabolism brought about by the infection, which is especially obvious when the organism is engaged in combating the infection. In severe terminal infections, however, the impaired general condition caused by inanition seems to be of significance. It is difficult to estimate to what extent the increased need for vitamin C which, in my cases, is typical of the stage of the disease when the wound is healing, raises the need of the organism for this vitamin. As several investigators have shown, vitamin C is of considerable importance for the healing of the wound. Hypo-

vitaminosis is accompanied by disturbance in the production of collagen, especially, and also that of intercellular substance (WOHLBACH 1933; NYLANDER 1940; HUNT 1941 et al.). The observation that in spite of the intake of vitamin C seasonal variation is detectable in some cases seems to point to the possibility that diet is of especial significance for the vitamin C household.

The reduction in the vitamin C amount of the serum *after operation*, in my cases, seems to be dependent on the severity of the operation and wound infection. BERSIN, LAUBER and NAFZIGER (1937) showed in their experimental investigations that major operations were followed by a decline in the vitamin C level. In their records of clinical studies BARTLETT, JONES and RYAN (1940) make similar statements. They also find that the patient's general condition is of especial importance.

Summary

On the basis of investigations carried out we could note in cases of chronic empyema of the pleura, as in other acute and chronic infectious diseases, a decline in the vitamin C level of the serum as compared with normal cases. In 34 cases who had not received vitamin C before the examination performed, the limit values were 0.11 and 0.72 mg. per 100 cc. Values below 0.40 mg. per 100 cc. occurred in 28 cases. Evidently the fluctuations in the serum vitamin C content were then also seasonal. The vitamin C deficiency in the organism was in these cases found to be greater, on an average, in the spring and in early summer. Symptoms of hypovitaminosis did not occur in any of the cases.

After operation the vitamin C level of the serum declined in 13 out of the 15 cases examined. The reduction was on an average 0.1 mg. per 100 cc. and most commonly took place on the 2nd—6th post-operative day. The pre-operative level was restored, however, within 1—4 weeks, when vitamin C was administered to the patients per os.

In severe cases of post-operative prolonged suppuration even considerable variation was noted in the vitamin C content of the serum. The limit values obtained in my investigations — zero and 1.44 mg. per 100 cc. — occurred in these cases. The lowest vitamin C concentration (zero) was encountered in two cases before death. These patients exhibited no symptoms of hypovitaminosis. In spite of the intake of vitamin C several patients showed values which were reduced in com-

parison with normal cases. Thus, in 15 out of 25 patients the value was below 0.40 mg. per 100 cc. in the first examination that was made. These patients, too, who had received vitamin C, exhibited some seasonal variation.

The deficiency of vitamin C produced in the organism is in my opinion primarily due to the increase in the metabolism caused by the severe infection. The rise in temperature which accompanies the infection seems to promote the decline in the vitamin C level in some cases.

IX

ON AMYLOID DEGENERATION IN CASES OF CHRONIC EMPYEMA OF THE PLEURA

SOME ASPECTS OF EARLIER STUDIES OF AMYLOID DEGENERATION

Theory of Amyloid Degeneration

The actual cause of amyloid degeneration and the way it originates have not yet been made clear. The chemical consistency of amyloid also remains a matter of speculation, although it is supposed to be an albumin with big molecules, evidently related to the globulins.

A number of different theories regarding the development of amyloid in the organism have been put forward, among which that of LETTERER (1926, 1934) and LOESCHKE (1927) has been most generally accepted. According to them *the deposition of amyloid is a consequence of the antigen-antibody reaction*. In typical amyloidosis the deposition seems to take place in connection with an antigen excess, not with the production of antibodies. The protein of the tissues or the leukocyte protein would then act as an antigen. APITZ (1940) attributes typical amyloid degeneration to a functional derangement of the cellular system of the body producing protein, which is due to the increased activity caused in the cells by infectious diseases.

Experimental investigations have shown that in animals different intoxications cause amyloid deposition, and that when the intoxication subsides the amyloid is resorbed. NOWAK (1898) was able to produce amyloid by turpentine oil and SCHEPILEWSKY (1899) by lab ferment. KUCZYNSKI (1923) fed animals with a large amount of food rich in protein (casein) or injected protein subcutaneously. By the last-mentioned method amyloid developed within between 10 to 30 days. When protein was administered by mouth, the results were less obvious. When the protein reserves of the animal were used up, the amyloid, too, disappeared. LETTERER (1926), among others, records similar findings. JAFFÉ (1926) studied the rôle played by fats, especially cholesterol, in experimental amyloidosis. He noted that mice when given food rich in

cholesterol required double the amount of nutrose before amyloid developed than the animals which had been on a diet poor in cholesterol. NIOSI (1937) produced amyloid degeneration in mice more easily after the removal of the spleen. Amyloid also occurs, as is well-known, in so called serum horses, in consequence of renewed injections of diphtheria toxin (HJÄRRE 1945).

It is a common feature of all these experimental studies that they occasion an absolute rise of the blood globulin content, as was demonstrated by EKLUND and REIMANN (1936) in corresponding investigations on rabbits. *Chronic hyperglobulinaemia thus seems to be an important factor in the production of amyloid. The deposition of the excess protein from the blood in the tissues produces amyloid, while the globulin content is reduced* (BEATTIE and DICKSON 1943).

The ratio of albumin and globulin in man shows only slight variation, being on an average 1.5:1 (SALVESEN 1926). In some infectious diseases with a rise of temperature and destruction of tissue a relative increase of globulin is often known to take place. Hyperglobulinaemia occurs most frequently in tuberculous patients whose globulin concentration shows increase at an active stage of the disease. The globulin level falls when the outlook for the patient improves (PETSCHACHER 1923). According to data submitted by BJÖRNEBOE and GORMSEN (1943) the rise in the serum globulin of immunized rats occurred contemporaneously with the development of antibodies. They declared that the increase in the globulin amount could be regarded as due to the production of antibodies. In recent literature hyperglobulinaemia is explained as being characterized by an increase of plasma cells and cells belonging to the reticulo-endothelial system, which makes one assume that the production of globulin is in some way connected with these cells (FLEISCHACKER 1940; APITZ 1940; RANSTRÖM 1946 et al.). Amyloid and hyperglobulinaemia are biological abnormalities occurring especially in infectious diseases. Yet it may be said that the change in the ratio of albumin and globulin and especially the increase of globulin is a common reaction of the organism, whose biological significance is not yet clear and which seems to be due to a number of various causes.

The lipid substances are closely related to the blood proteins and form with them so-called lipoproteins. They have been shown to be primarily present in α - and β -globulins, while the γ -globulins contain mainly antibodies. The most common lipid components, in these cases, are cholesterol, phospholipids and free fatty acids (BLIX, TISELIUS and SVENSSON 1941). Among lipid substances cholesterol metabolism, especially, has been investigated in different diseases. Thus v. GIERKEN (1936) noted hypercholesterolaemia in cases of nephrosis, nephritis, diabetes, liver cirrhosis, obstructive jaundice and in allergic diseases. Hypocholesterolaemia, on the other hand, was present in suppurative conditions, infectious diseases, in association with tumours, in acute yellow liver atrophy and in anaemia. EICHELBERGER and McGLUSKEY (1927) declared that increase of cholesterol in

tuberculosis indicates power of resistance and immunity, while hypocholesterolaemia is a sign of a decline of these characteristics. Especially in nephrotic conditions high values may occur, varying between 300 and 1000 mg. per 100 cc. (STEINER and DOMANSKI 1942). VESA and T. KALAJA (1939), T. KALAJA and HELVE (1947) noted elevated values of the lipid phosphorus of the serum in cases of nephritis. In cases of amyloid nephrosis as in other nephrotic conditions a great many investigators have noted hypercholesterolaemia, which, however, is of a less severe character (LICHTENSTEIN and EPSTEIN 1931; JOHANSSON 1945). JOHANSSON (1946) investigated in cases of amyloid nephrosis in addition to the plasma cholesterol also the total fat amount. In 12 cases in all, with a cholesterol level from 100 to 600 mg. per 100 cc. (normal level 170—294 mg. per 100 cc.), the total fat content of the plasma varied roughly from 600 to 2000 mg. per 100 cc. (normal 519—951 mg. per 100 cc.). In his opinion the increase of lipids in the plasma compensated the contemporaneous lowering of the colloid osmotic pressure which is due to hypalbuminaemia. This assumption, however, has been contradicted by certain cases where in spite of hypalbuminaemia neither hypercholesterolaemia nor lipaemia was present. Besides increased and normal cholesterol and total lipid amounts also subnormal values were noted in some cases, especially before death.

Diagnosis

The diagnosis of amyloidosis is difficult and often open to some question, especially in cases where there is no albumin in the urine and no enlargement of the liver or the spleen is noted. This type of amyloid deposition is called by WIDAL «quiescent» amyloidosis — une forme complètement muette. By the side of the diagnosis confirming amyloidosis by a histological examination of a specimen obtained by puncture from the liver and the spleen, the Congo red test is of great practical significance. It seems that in spite of negative organic punctures the presence of amyloid cannot be ruled out with certainty. JOSEFSON was the first to make spleen punctures, in 1917, and in 1928 WALDENSTRÖM published his study of liver punctures in amyloid patients.

The Congo red test was discovered accidentally by BENNHOLD in 1923 when he was making determinations of the blood volume by means of the technique of KEITH, ROWNTREE and GERAGHTY (1915), in which he used Congo red as a dye. He observed that in some patients the dye disappeared completely from the blood. When one of these cases was subjected to autopsy, far-advanced amyloid degeneration was disclosed in the liver and in the spleen. On the basis of these findings BENNHOLD published his diagnostic procedure which was mentioned earlier.

BENNHOLD (1923) investigated the disappearance of Congo red from the blood also in various other pathological conditions. The amount of dye

which normally (11—30 per cent) disappeared within one hour, he called the Congo red index. In glomerulonephritis and nephrosclerosis (15 cases) he obtained normal values. In diseases of the liver the disappearance of the dye from the serum was delayed. In two disease groups the dye disappeared from the blood more rapidly than in others, namely in tubular nephritis (nephrosis) and in pulmonary tuberculosis. Two of the four cases affected with the former disease were luetic. The Congo red index of these patients ranged between 47 and 55 per cent. Of the nine patients with pulmonary tuberculosis 6 had amyloidosis, in the majority of whom the dye was absorbed completely within an hour. In the tuberculous cases without amyloidosis the values were normal. As a result of his investigations BENNHOLD declared that the disappearance of 60 per cent or more of the dye was an evident sign of amyloid degeneration. Values ranging between 40 and 60 per cent pointed either to amyloidosis or nephrosis. He also declared that in all the cases where the Congo red index was 100 per cent, far-advanced amyloidosis of the liver was present.

The rapid disappearance of the dye from the liver in amyloid disease was attributed by BENNHOLD (1924) primarily to the absorptive capacity of the amyloid substance, but the serum was also of considerable significance in this phenomenon. In amyloid disease as in nephrotic conditions with severe albuminuria the capacity of the plasma to absorb Congo red is reduced, which is evidently due to changed quantitative ratios in the plasma. In amyloid cases BENNHOLD had discovered dye in the organs after death, but not in other cases when the test was made shortly before death.

Numerous investigators have been able to confirm BENNHOLD's findings in clinical investigations, and they regard the Congo red test as a reliable means for diagnosing amyloidosis.

Thus PAUNZ (1924) modified BENNHOLD's procedure by using the smallest possible amount of 0.6 per cent Congo red solution in order to make the absorption of the dye in amyloid cases as complete as possible. He injected 2 cc. of this solution per kilogram of body weight and examined, in addition, the urine before and after the test. By comparing the serum of the samples before the injection and one hour after it he could ascertain whether there was any dye left. When one drop of concentrated hydrochloric acid is added, a white sediment is formed which in the presence of even the slightest amount of the dye turns blue (negative result). In all the investigated cases with a positive test amyloidosis was also established at autopsy. KOREF (1924), SCHÖNBERGER and ROSENBLATT (1925) carried out their investigations by Bennhold's technique and were able to fully corroborate his findings. The two last-mentioned investigators found that in cases of nephrosis the urine contained dye after half an hour, while chronic cases of nephritis did not differ from the normal. They also declared that in infections (pneumonia, pulmonary abscess, endocarditis, polyserositis etc.), where as in nephrotic conditions the blood contains a larger amount of globulins, dye was also present

in the urine. In diseases of the liver and in cases with malignant tumours the values were normal. The 30 patients examined did not exhibit any disturbance in connection with the injections. NÉMETH (1926) and NATHAN (1928), also, using PAUNZ' modification, and BOOKMAN and ROSENTHAL (1927) by means of BENNHOLD's procedure, confirmed the findings of earlier investigators. The two last-mentioned established a slightly higher level in tuberculous patients and declared that a Congo red index above 60 per cent was indicative of amyloidosis. Yet even lower values did not rule out the possibility of amyloid.

M. CH. EHRSTRÖM (1936) investigated the changed physical characteristics of the plasma proteins especially in nephrotic conditions. He recorded as his view that in these cases the Congo red is excreted in the urine and combines with the urinary albumin. Although the albumin absorbs in these cases a certain amount of the dye from the blood, the disappearance of the Congo red from the blood is not solely attributable to this fact. Instead, in nephric diseases with severe albuminuria the positive Congo red test is due to the reduced absorptive capacity of the plasma.

LIPSTEIN (1938) performed Congo red tests by BENNHOLD's method in patients affected with pulmonary tuberculosis and compared the findings with observations made later at autopsy. In 24 out of 34 patients who had amyloidosis the dye disappeared completely. Five showed a Congo red index exceeding 90 per cent, in the rest it varied from 35 to 82 per cent. Among 91 tuberculous patients without concomitant amyloidosis the disappearance of the dye was below 50 per cent in 61 cases, between 51 and 75 per cent in 26 cases, and in 4 cases between 80 and 100 per cent. There has been no satisfactory explanation to account for the circumstance that the disappearance of the dye may be total. Yet certain significance has been attributed to the increased activity of the reticulo-endothelial system.

TARAN and ECKSTEIN (1942), also, report on a modification to BENNHOLD's method, according to which the disappearance from the blood of the dye in amyloid cases varies between 90 and 100 per cent. They employed 1 cc. of 1 per cent Congo red solution to 10 pounds of body weight. Following the injection a sample was taken after two minutes and another after one hour, and acetone was added to the serum obtained to eliminate possible haemolysis. When comparing the serum samples obtained after two minutes with those taken after four minutes the disappearance of part of the dye as early as this could be noted in cases of amyloidosis. They consequently used the sample taken after two minutes as a standard solution. Autopsy could be performed on 20 out of 110 of the patients, in whom the Congo test was negative. Only one of them exhibited amyloidosis, the Congo red index being according to their modified technique 65 per cent about 4 $\frac{1}{2}$ months before death.

JOHANSSON (1945), who used BENNHOLD's original method, regards 35—45 per cent as normal values, and for the rest reports findings which are in agreement with those presented by BENNHOLD.

Possible Disappearance of Amyloid

Resorption of amyloid is of extreme rarity. Only few records of such cases have appeared in the literature. Before the Congo red test was introduced as a diagnostic medium, isolated cases of regression were noted by KRETZSCHMAR and WESTBROOK (1880) and GARDNER (1891). In these cases the diagnosis was based only on clinical symptoms, so that they may be held open to some question.

WALDENSTRÖM (1928) was the first to report reversal of amyloidosis after having subjected specimens obtained by puncture to histological examination. In three patients with bone tuberculosis the amyloid disappeared completely from the liver after surgical treatment. WALDENSTRÖM lays especial emphasis on the significance of the purulent discharge for the development of the amyloid degeneration. If the suppurating fistulas can be eliminated before the general condition of the patient has become severely impaired, the amyloid will subside. The deposition of amyloid takes place contemporaneously with the pus formation. If the latter cannot be suppressed, the amyloid cannot be got rid of. The period of suppuration during which the amyloidosis develops is according to him on an average 1—2 years. The species of the bacteria does not seem to be important.

WHITBECK (1932) used the Congo red test as a diagnostic medium. Of 7 patients with bone tuberculosis, in whom the dye disappeared from the serum entirely within an hour, 5 recovered completely after 18 months of clinical treatment. Along with a diminution of the size of the liver and the spleen the Congo red index fell. In the case recorded by HABEIN (1934), with a suppurating wound in the axillary tract, the Congo red test was likewise positive, and the liver and the spleen enlarged. When the suppuration was brought to an end the symptoms disappeared and the patient was restored to complete health. REIMANN (1935) and ROSENBLATT (1936) both brought out reports of amyloid resorption in a tuberculous patient, likewise GRAYZELL and JACOBI (1938) in a case of pyogenic osteomyelitis. In all these cases a 100 per cent disappearance of the dye in the Congo red test along with certain clinical symptoms was noted. In the case recorded by ROSENBLATT it is of especial interest that recovery took place in spite of oedema. The presence of oedema in cases of amyloidosis is a very severe prognostic symptom, as was pointed out e.g. by PEARLMAN (1940). The last-mentioned investigator has reported regression of amyloidosis in four patients with pulmonary tuberculosis. In these cases the liver and the spleen were enlarged, the urine contained albumin and casts. The Congo red index, in addition, was 100 per cent. When the patients who were under clinical treatment recovered, the urinary albumin disappeared.

OWN INVESTIGATIONS ON CASES OF AMYLOID DEGENERATION WHICH
DEVELOPED IN CONNECTION WITH CASES OF CHRONIC
EMPYEMA OF THE PLEURA

To diagnosticate possible development of amyloid in cases of chronic empyema of the pleura I undertook Congo red tests especially in such cases in which the clinical symptoms seemed to point to amyloid degeneration¹. In addition, I performed punctures of the liver. 7 out of 59 cases of chronic empyema exhibited amyloid degeneration (1, 4, 5, 8, 25, 26 and 27; Table 10). The age of these patients varied between 23 and 42 years, the average age being 33 years. In four cases (4, 5, 26 and 27) the clinical diagnosis was corroborated either by means of a liver puncture or at autopsy. Two cases were diagnosed by means of the Congo red test only² (Nos. 1 and 8), and in one case no amyloid degeneration was disclosed until autopsy (No. 25). The liver was notably enlarged only in Case 4. Urinary albumin was present in all except Case 1. Pathological sediment in the urine (epithelial cells, leukocytes, hyaline and granular casts) occurred especially in Case 8.

Evident recovery was made by one patient (Case 1), and one (Case 8) is still under treatment. The amyloid cases were patients with traumatic chronic empyema of the pleura except two, of which one (Case 4) had a tuberculous and one (Case 26) a metapneumonic chronic empyema.

In six out of these seven cases of amyloid degeneration (Nos. 1, 4, 5, 8, 26 and 27) I undertook besides Congo red tests also determinations of the serum albumin and globulin and investigations of the lipid metabolism of the plasma (Table 11). Owing to post-war conditions all the investigations could not be carried out according to plan. The total cholesterol of the plasma was determined in all the cases. The cholesterol ester was examined in three and the lipid phosphorus in two cases. A quantitative determination of the urinary albumin was made in four cases.

The *comparative material* for those of my of amyloid cases which developed in connection with chronic suppuration of the pleura consisted of 5 other amyloid cases (Nos. 90—94, Tables 10 and 11). Chronic osteomyelitis

¹ Complications did not occur in any of the cases at the injection of the Congo red solution.

² After the completion of the manuscript amyloid was disclosed at autopsy in Case 8.

was the primary disease in one of these cases (No. 90), actinomycosis in one (Case 91), in one tuberculous empyema and peritonitis (Case 94), and bronchiectasis in two of the cases (Nos. 92 and 93). Corresponding examinations were carried out also in 9 cases of chronic empyema, where no amyloid degeneration was present (Table 12).

The Congo Red Test

The results of my investigations are shown in Table 10. The values obtained in the Congo red test in cases of amyloidosis which developed in connection with chronic empyema of the pleura show marked variation. In Cases 4, 5, 26 and 27, which were corroborated by means of liver punctures or at autopsy, the Congo red index fluctuated between 56 and 100 per cent. In case 1 the higher values 77 and 66 per cent occurred at the two first tests, likewise in Case 8 in the three last tests, the Congo red index being 60, 63 and 75 per cent.

In the amyloid cases of the *comparative material* (Table 10; Cases 90—94) the Congo red index varied between 65 and 100 per cent. Urinary albumin was present in each of these cases. In the cases (Nos. 91 and 93) showing the lowest percentages (67 and 65 per cent), the diagnosis could be confirmed at autopsy. The Congo red index values obtained in these cases are thus in full agreement with those obtained in cases of amyloid degeneration which developed in consequence of chronic suppuration of the pleura. Table 12 presents the findings of the Congo red tests carried out in 9 cases of chronic empyema of the pleura. The limit values were 21 and 56 per cent, both of them occurring in Case 2, where the chronic metapneumonic empyema was complicated by tuberculosis. When in this case the Congo index was 48 per cent, no amyloid was disclosed in the puncture specimen from the liver.

In Cases 11, 20, 23 and 56, which do not appear in Table 14, the disappearance of the dye from the serum within 1 hour was 14, 26, 36 and 31 per cent.

On the basis of the foregoing we may state that the Congo red index varied between 60 and 100 per cent in those cases of amyloid degeneration where the clinical diagnosis had been confirmed by means of a liver puncture or at autopsy. Yet one case showed values below 60 per cent (56 and 57 per cent). My findings are thus in keeping with those recorded e.g. by BENNOLD (1923) and HARRISON (1947), according to which a 60 per cent or more Congo red test value

TABLE 10

CONGO RED TEST IN CASES WITH AMYLOIDOSIS. PERIOD OF SUPPURATION BEFORE THE FIRST CONGO RED TEST AND BEFORE ALBUMIN WAS TRACED IN THE URINE. THE OCCURRENCE OF AMYLOID DEGENERATION IN DIFFERENT ORGANS

(P₁ = period of suppuration before the Congo red test, in years. P₂ = period of suppuration before albumin was traced in the urine, in years. C.R.I. = percentage of Congo red which disappeared from the blood within 1 hour. LP = liver puncture; L = liver; S = spleen; K = kidney; SG = suprarenal gland. Nos. 90—94 are cases of amyloidosis belonging to the comparative material.)

No.	Date of test	P ₁	P ₂	Date of exitus	C.R.I.	LP	Alb. in urine 0/00	L	S	K	SG	
1	Chronic empyema of the pleura:		---		77	---	---					
	8/9. 45	ca. 2 ½										
	10/10. 45											
	23/11. 45 ¹											
	27/3. 46 ¹											
	3/5. 46 ¹											
	15 5. 46 ¹											
4	12/6. 45	ca. 2	ca. 1		63	+	4.5					
	17/9. 45				78		+					
	28/11. 45				97		+					
	7/3. 46				100		5.0					
	27/3. 46				57		10.0					
	24/4. 46				60		5.5					
	7/5. 46						+					+
	12/6. 46				95		4.5					
	22/3. 47				56		5.0					
	24/11. 47				11/12. 47		87					+
5	2/8. 45	ca. 1/12	ca. 7/12	6/2. 46	30		---	+	+++	++	++	
	1/2. 46	ca. 7/12			79		2.5					
8	27/5. 46 ²	ca. 11/12	ca. 1 ½		22		---					
	14/2. 47	ca. 1 7/12			60		3.5					
	5/3. 47				63		5.4					
	8/4. 47				75		12.0					
25	30/6. 45		ca. 11/12	27/8. 45			0.75	+	++	---	--	
	16/8. 45						---					
26	16/6. 45	ca. 1 5/12	ca. 1 2/12	28/6. 45	63		10.0	---	+++	++	+	
							+					
27	17/6. 45	ca. 1	ca. 11/12	7/8. 45	96		10.0		+++	+++	---	
	11/7. 45				99		+					

¹ = Date when the amyloid had evidently been resorbed.

² = Date when the amyloid had evidently not yet formed.

TABLE 10 (Continued)

No.	Date of test	P ₁	P ₂	Date of exitus	C.R.I.	LP	Alb. in urine ‰	L	S	K	SG
90	Other chronic suppurative cases: 4/2. 46 13/3. 46 27/3. 46 29/4. 46	ca. 7	ca. 2		81 86 75 100		6.0 3.5 1.0 +				
91	1/2. 46	ca. 6 ½		22/2. 46	67		6.5	+	+	+	
92	12/6. 46	ca. 11			80		6.3				
93	5/3. 47 22/3. 47	ca. 4		21/4. 47	65 83		2.5 1.5	+	+++	+++	
94	14/3. 47	ca. 1			95		ca. 18				

affords proof of evident amyloidosis. I therefore find myself justified in claiming that we have to do with amyloid degeneration also in Cases 1 and 8. The former patient showed in the two first tests values 77 and 66 per cent, the latter in the three last examinations 60, 63 and 70 per cent respectively. In Case 1 the suppuration had persisted for more than two years, and the sedimentation rate of the blood varied around 100. Neither urinary albumin nor any other clinical symptoms of amyloidosis were present. Case 8, on the other hand, exhibited albumin and pathological sediment in the urine.

In one case (No. 4), which was under observation for nearly two years, the results of the Congo red test showed marked variation. We may assume from this that the formation of the amyloid is a comparatively acute process. The disappearance of the dye from the blood is primarily dependent upon the stage of the amyloid degeneration in different organs.

In cases of chronic empyema of the pleura without symptoms of amyloidosis, the limit values of the Congo red index were 14 and 47 per cent in 11 examined patients out of 13. Only in two cases the values exceed 50 per cent, the highest, 56 per cent, occurring in a tuberculous case of empyema.

Clinical Survey of Amyloid Cases

The *resorption of amyloid* seems probable in Case 1. This case, who had no clinical symptoms of amyloidosis, will be presented in the following:

Case 1. Corporal, 31 years old. The patient was wounded by shell splinters in the left lung 4/2 43. *Revisio vulneris* and *suturatio pleurae* were carried out at the field hospital. Haemothorax developed on the left side and later suppurating pleuritis, on account of which thoracostomy was undertaken 11/3 43. To control recurrent suppuration and temperature (ad 40° C) renewed drainage of the pleura was instituted after about 6 months. 4/11 43 the patient was admitted to our hospital. — *Status praesens* was as follows: General condition fairly satisfactory. No temperature. A suppurating fistula in the left side. The amount of daily discharge withdrawn by suction is about 100—200 cc. Lungs: Right 0. The left half of the chest does not move at all when breathing. The breathing sound is impaired and a complete depression at the beck reaching the height of the fistula. X-ray studies show two metal splinters in the left lung, and a total empyema cavity at the bottom of which there is a fluid surface. The heart and the mediastinum have shifted to the right. Vit. cap. 2400. No tubercle bacilli in the sputum. Haemoglobin 73, sedimentation rate 160 mm/1 h., WaR —, Kahn —. Urinary alb. —, Nyl. —. When the suppurative discharge diminished, the sedimentation rate continued high, varying from 49 to 113 mm./1 h. — 27/1 44 *extractio corp. al. pulm. sin.* was carried out. Following this the patient remained under treatment for nearly half a year at another hospital. There he had persistent temperature rising to 39° C, and the sedimentation rate was still high, varying from 65 to 11 mm./1 h. — 14/6 44 the patient returned to our hospital. The general condition was distinctly worse. The empyema cavity was of former size but very open. An abundance of evil-smelling discharge was secreted. From 10/11 44 to 6/6 45 five operations were carried out to eliminate the pleural cavity.

8/9 45, when the suppuration had continued for about two and a half years, the Congo red index was 77 per cent. The *status praesens* was at the time as follows: General condition fairly satisfactory. No temperature. In the left side a suppurating surface of the size of a large palm extends from the lower edge of the shoulder-blade up to the axilla, the bottom of which is the markedly thickened pleura visceralis. The suppurative discharge is rather abundant. The heart was regular in outline, and normal in size. There were no murmurs. X-ray studies showed a complete collapse of the left lung and a marked shift of the heart and the mediastinum to the right. Vit. cap. 1600. No tubercle bacilli in the sputum. The liver and the spleen had not enlarged noticeably. Haemoglobin 56, leuk. 6,800, sedimentation rate 103 mm./1 h., non-protein nitrogen 30 mg. per 100 cc. Urinary albumin —, Nyl. —. Specimen of discharge from the wound: Gram-negative rods in staining, and *B. proteus* growing in the culture. Löwenstein —. While the suppuration diminished slowly the extent of the wound remained almost unchanged during several months. Along with an improvement

of the general condition the sedimentation rate and the Congo red index fell. About one month since the first test the disappearance of the dye from the serum within 1 hour was 66 per cent and about one month and a half later 46 per cent. The corresponding blood sedimentation rates were 95 and 75 mm./1 h. About 8 months from the first test the Congo red test was 27 per cent and the sedimentation rate 57 mm./1 h. The wound had then closed noticeably and the suppuration was negligible. No amyloid was disclosed in the liver puncture.

Comment: In consequence of chronic empyema a soldier who had been wounded in the left lung developed evident amyloidosis without typical clinical symptoms. After operations carried out, while the suppuration lasted, the blood sedimentation rate remained high, varying under and above 100 mm. 1 h. When the suppuration had continued for about 2 $\frac{1}{2}$ years, the Congo red index was found to be 77 and 66 per cent in two tests made with an interval of about 1 month. After about 1 $\frac{1}{2}$ months, and also in examinations undertaken later, the general condition showing marked improvement, the Congo red index was normal, evidently indicative of resorption of the amyloid.

When comparing the findings with other Congo red index values obtained in my amyloid cases we may assume, in this case, amyloidosis, which however has been resorbed. Hyperglobulinaemia, as we know, is usually a condition concurrent with amyloid degeneration, causing a more or less increased sedimentation rate of the blood. It is, however, probable, that in this case the high sedimentation rate was primarily due to the severe infection. Yet it was established that along with a fall in the Congo red index the blood sedimentation rate also showed a fall.

Another case of amyloidosis of the same type as the one just reviewed will be described in the following. No Congo red tests were carried out in this case, but amyloid degeneration was revealed at autopsy.

Case 25. Sergeant, aged 23 years. The patient was wounded 25/6 44 by a shell splinter in the left lung and developed in consequence empyema of the pleura. Thoracostomy was performed 19/7 44. Abundant secretion of discharge took place and a bronchial fistula was noted. He came up for treatment at our hospital 20/11 44. *Status praesens* was then as follows: Fair general condition. No fever. A suppurating fistula, 7 cm. in depth, was noted in the left side. The heart was regular in outline and normal in size. There was no murmur. X-ray studies show that the left half of the dia-

phragm has risen and adheres to the left wall of the chest. The sinus is shadowed. Slight pleural infiltration but no fluid surface. In the apical field and the intraclavicular region intense shadowing, which may be due to pleural infiltration caused by the empyema, but we may also have to deal with an encapsulated empyema. A shadow of the splinter is visible at the height of 2nd rib. Right lung: 0. Vit. cap. 2700. No tubercle bacilli in the sputum, Löwenstein —. Urinary alb. —, Nyl. —. An operation was carried out 2/12 44, but no empyema was disclosed. About 3 weeks later the patient contracted diphtheria, after which cardiac symptoms manifested themselves and systolic murmur was noted. Vague gastric discomfort pointing to gastritis also appeared. However, the patient recovered completely and was allowed home leave. He returned to the hospital 27/4 45. By that time a suppurating fistula had formed on the scar of the thoracostomy. The patient also had a rise in temperature. About one week later he had an attack of severe haemoptysis, and about 120 cc. of blood was ejected. High temperature was registered during three days, varying between 39.5° and 40.5° C. Symptoms pointing to mediastinitis developed and swallowing was difficult, on account of which gastrostomy was performed. The general condition was then poor. Gradually symptoms indicative of pericarditis set in, but the puncture of the pericardium was negative. The haemoglobin was 49 and the sedimentation rate 133 mm./1 h. While the temperature remained high, a drain was introduced 22/5 45 into the pleural cavity. After the suppuration had lasted, with short intervals, for about 11 months, opalescence indicative of albumin was noted for the first time during a high fever period (38°—39° C) in June, 1945. The liver and the spleen did not then show any noticeable enlargement. As the fever and the suppuration persisted, the pleural empyema was opened totally 3/8 45. The general condition, however, declined, and breathing became difficult. The cardiac function was irregular and arrhythmia and oedema were noted. In spite of numerous blood transfusions the haemoglobin value remained low, varying from 43 to 56. Urinary albumin occurred at times towards the terminal stage of the disease. About 2 months before death (27/8 45) the Esbach was 0.70‰. During the last 3 weeks no albumin was present in the urine.

Diagnosis at autopsy: Pyopneumothorax chr. l. sin. Atelectasis pulm. sin. Pneumonia lobaris lobi inf. l. a. Empyema pleurae l.dx. Pericarditis et concretio pericardii. Hypertrophia et myodegeneratio cordis. Stasis hepatis. Amyloidosis hepatis et lienis. Enteritis. Stat. post thoracoplastiam.

Histological examination. No amyloid was disclosed in the kidneys. The tubules showed disintegration. Nephrosis. Brownish mass, which was amyloid, was detected in the liver on the outer cell surface. Post-mortal changes were present, in addition. Congestion and amyloid degeneration were noted in the spleen.

Comment: A soldier wounded in the left lung developed chronic empyema. He contracted diphtheria which was accompanied by

cardiac symptoms. About 10 months after being wounded the patient had a severe attack of haemorrhage of the lungs, evidently due to the splinter, which was followed by bronchopneumonia. Symptoms pointing to mediastinitis and pericarditis ensued, and the patient had fever during nearly 4 months. During the last two months slight albuminuria was occasionally present. About 14 months after the patient had been wounded amyloid was disclosed at autopsy in the spleen and the liver, but not in the kidneys.

In the case reviewed the intermittent slight albuminuria occurring at the terminal stage of the disease might possibly be ascribed — from the clinical point of view — to the rise of temperature. However, the histological examination made in connection with the autopsy established nephrosis, though no amyloid was detected in the kidneys.

I now proceed to review a case which serves to illustrate, in my opinion, the significance of the liver puncture in the diagnosis of amyloid degeneration.

Case 4. Sergeant major, 42 years. The patient fell ill with right-side pneumonia in June, 1943, after which empyema of the pleura developed. Thoracostomy was carried out 30/6 43. Specimen of wound discharge: An abundance of leukocytes, streptococcus haemolyticus growing in the culture, Löwenstein —. In August, 1943 a second thoracostomy was carried out. The general condition was then markedly poor, and the patient had exhibited a rise of temperature and abundant suppuration. The X-ray photograph revealed low down on the right, laterally, a small empyema cavity. On account of chronic empyema thoracoplasty was undertaken 4/12 43. While the suppuration continued, bronchial fistulas developed. *In June 1944 albumin began to appear in the urine* (Esbach 5‰). The patient was then admitted for treatment at the Chest Surgery Department. In November 1944 another thoracoplasty followed, after which the bronchial fistulas closed, the general condition improved, but an extensive area with an exposed surface of the lung still remained. Abundant albumin was present in the urine (Esbach 16‰).

At an examination made 12/6 45, prior to which the suppuration had been persisting for 2 years and albumin had appeared in the urine for about one year, the Congo red index was 63 per cent. The *status praesens* was then as follows: General condition fairly satisfactory. The temperature was normal. At the back, on the right, bordering on the medial edge of the shoulder-blade, a shallow suppurating wound surface about the size of the palm, which granulated feebly. On account of operations the right half of the chest had fallen in. X-ray studies showed a marked collapse of the right lung

following thoracoplasty. Changes indicative of tuberculosis were revealed in both lungs. No tubercle bacilli in the sputum. The heart was regular in outline and normal in size. There were no murmurs. No noticeable enlargement of either the liver or of the spleen. S.R. 116 mm/1 h., haemoglobin 68, leuk. 10.500, WR —, Kahn —. Albumin in the urine (Esbach 4.5‰). Sediment: Erythrocytes and leukocytes comparatively numerous, some epithelial cells and granular casts. Discharge specimen from the wound: Gram-negative rods, streptococcus haemolyticus grew in the culture, Löwenstein —. In July, 1945 a new operation was performed, after which the wound nevertheless kept suppurating. Yet the general condition of the patient showed noticeable improvement and he was allowed home leave about two months later. The Congo red index was then 78 per cent, while the urinary albumin remained relatively abundant. About 9 months after the first test the Congo red index was 100 per cent (7/3 46), but ca. 3 and 6 weeks later 57 and 60 per cent. By then the liver had enlarged somewhat, the lower edge being on the right about 1½ fingerbreadths below the costal arch. *In the biopsy specimen obtained by means of liver puncture (7/5 46) slight amyloid degeneration was established histologically* (at the Department of Pathoanatomy, University of Helsinki, by prof. SAXÉN). In the test performed about one month later the Congo red index was 65 per cent and the albumin level of the urine 4.5‰ (Esbach). 22/3 47 the suppuration had terminated, the wound was almost completely closed and the general condition had improved to such an extent that the patient had been working, for about 8½ months in his former occupation as a janitor. *The liver was restored to normal size and no amyloid was present in the biopsy specimen obtained by liver puncture.* Yet there was still albumin in the urine (5‰). About 7½ months later the patient, however, died at another hospital.

Diagnosis at autopsy: Tuberculosis pulm. l.a. Fistula post thoracoplastiam l.dx. Amyloidosis hepatis et renum. Thrombosis v. renalis l.sin.

Comment: A patient who was 42 years of age exhibited in consequence of chronic empyema of the pleura amyloid degeneration. When the suppuration had continued for nearly three years, the characteristic clinical symptoms (albuminuria, enlargement of the liver) were accompanied by a 100 per cent Congo red index. Histologically, amyloid was disclosed in the biopsy specimen obtained from the liver. Tests renewed about 10½ months later did not show amyloid degeneration in the liver tissue, and the Congo red index had fallen down to 56 per cent. The liver was then no longer enlarged. 7½ months after the last-mentioned test the patient died, and amyloid was noted in the liver and in the kidneys.

In this case it could be supposed after the examination in which no amyloid was detected in the histological specimen obtained by

liver puncture, that the amyloid had been resorbed. Especially the disappearance of the hepatic oedema and the marked bettering of the general condition, so that the patient was able to resume his former occupation, seemed to speak in favour of this theory. When considering, however, that the patient was suffering from severe, far-advanced progressive pulmonary tuberculosis, as was established at autopsy, amyloid may most likely have been present all the time. The continuous appearance of abundant albumin in the urine was additional evidence.

The liver puncture seems to be of especial importance for the diagnosis of amyloid in such instances when amyloid is disclosed in the histological examination. On the other hand, negative findings in the biopsy specimen evidently do not rule out the possibility of amyloidosis even in the liver. Amyloid is first deposited in the intermediary part of the lobules, and it is only when a large amount of amyloid has developed that the entire lobule may be filled with amyloid substance. Nor does the amyloid degeneration take place evenly throughout the liver. It therefore seems evident that if there is only little amyloid present one may, when performing the liver puncture, strike a region where there is no amyloid.

In cases of amyloidosis which had developed in connection with chronic empyema of the pleura, the *length of the suppurative period* varied, before the first positive Congo red test (over 60 per cent) or before autopsy, from 7 months to 2 ½ years (Table 10). In Cases 1, 4, 26 and 27 the amyloid appears to have developed before the investigations had been started. The suppurative period was then in Case 1 2 ½ years, and in Cases 4, 26 and 27 about 2 years, 1 5/12 and 1 year respectively. In Case 5, developing empyema in connection with recurrent chronic haemothorax, the Congo red index was 30 per cent about one month later. No albumin occurred in this instance in the urine, and there was none present about 3 ½ months later when the patient was discharged. When the supuration had been continuing for about 7 months, the patient was re-admitted to the hospital. Amyloidosis was then indicated by albuminuria and an elevated Congo red index, which was 79 per cent. At autopsy amyloid was revealed in the liver, the spleen, the kidneys and the adrenals. In Case 8 the patient, who after having been wounded developed haemothorax and afterwards a so-called encapsulated empyema, had a Congo red index of 22 per

cent about 2 years later. Before this the suppuration from the opened empyema cavity had persisted for about 11 months. About 8 $\frac{1}{2}$ months afterwards, while the suppuration was still continuing, the Congo red index was 60 per cent, and albumin had occurred in the urine already for about 1 $\frac{1}{2}$ months. With the urinary albumin (Esbach 3.5 $\frac{0}{100}$) pathological sediment, such as epithelial cells, leukocytes, hyaline and granular casts, was disclosed, in addition. In Case 25 amyloid was diagnosed at autopsy after a suppurative period of about 14 months. Provided that the albuminuria can be regarded as an absolute symptom of the amyloidosis which had developed in these cases, the corresponding suppurative period varied from about 7 to 18 months (Table 10). In Case 4 it was 12 months and in Cases 5, 8, 25, 26 and 27 about 7, 18, 11, 14 and 11 months respectively.

In several other cases of empyema the suppuration had lasted much longer without amyloidosis having been established. Thus in Cases 22, 23 and 56 the period in question had been about 5 $\frac{1}{2}$, 4 $\frac{1}{2}$ and 13 years. No significant differences were noted in the ages of the patients. Nor did the various types of bacteria seem to be of any especial significance here. *The persistent fever recorded in connection with the suppuration, on the other hand, may have had a promotive effect on the development of the amyloid.* This appeared likely in Cases 5 and 25, where the febrile condition lasted for several months.

Localization did not seem to have any effect upon the incidence of amyloid. Amyloid occurred in these established cases, as usually in general amyloidosis, in the parenchymatous organs of the abdominal cavity.

Quantitative Relations of Serum Proteins

The results of my investigations are shown in Table 11. In amyloid cases which developed in connection with chronic empyema of the pleura (Nos. 1, 4, 5, 8, 26 and 27) the total proteins varied between 4.9 and 7.2 per cent, the relative albumin amount being from 26.5 to 52.6 per cent of the total protein. The albumin percentage ranged between 1.3 and 3.1 per cent, and the globulin correspondingly from 2.5 to 4.6 per cent.

TABLE 11

SERUM PROTEINS AND PLASMA LIPIDS AND URINARY ALBUMIN IN AMYLOID DEGENERATION. THE PLASMA LIPIDS IN NORMAL CASES ACCORDING TO HELVE (1947)

(C = Total cholesterol; Ce = Cholesterol esters; Tlp = Total lipid phosphorus; P = Total phosphatides [$25 \times$ Tlp value]; Ce/C = Relative proportion of ester cholesterol to total cholesterol; P/C = Relative proportion of phosphatides to total cholesterol. Nos. 90—94 are cases of amyloidosis belonging to the comparative material.)

No.	Date of test	S e r u m				P l a s m a						U r i n e			
		Total protein %	Albumin %	Globulin %	Relative albumin %	C mg %	Ce mg %	Tlp mg %	P mg %	Ce/C %	P/C %	Total protein %	Albumin %	Globulin %	Relative albumin %
Cases of chronic empyema of the pleur.:															
1	14/9. 45	6.8				209						—			
	10/10. 45	6.5	2.6	* 3.9	40.0							—			
	27/3. 46 ¹	6.7	3.8	2.9	56.7	137	96			70		—			
	3/5. 46 ¹	6.8	3.7	3.1	52.9	144	78			54		—			
	20/6. 46 ¹	7.5	3.9	3.6	52.0	234	109	18.8	470	47	201	—			
	19/9. 46 ¹					183	117	9.4	235	64	128	—			
4	12/6. 45	5.8				225						6.0	3.9	2.1	65.0
	25/9. 45	5.6				438						+			
	27/3. 46	5.2	2.7	2.5	51.9	285	162			57		9.2			
	24/4. 46	6.3	3.1	3.2	49.2	273	137			50		8.7			
	8/5. 46	5.7	3.0	2.7	52.6	385	185			48		+			
	12/6. 46	5.6	2.6	3.0	46.4	461	246	13.5	338	51	73	+			
5	22/3. 47	7.2	2.6	4.6	36.1	234	115	14.8	370	49	158	4.6	4.5	0.1	97.8
	5 2. 46	6.0	1.8	4.2	30.0	420	86			20		10.4			

8	27/5. 46 ² 15/6. 46 ² 11/3. 47 22/3. 47	7.1 7.5 7.0 5.8	4.6 2.7 2.8	2.5 4.3 3.0	64.8 38.6 48.3	234 226 148	207 141 111	12.5 14.0 10.5	313 350 263	88 62 75	133 155 177	— — 6.8 9.2	— — 6.3 8.6	— — 0.5 0.6	— — 92.6 93.5
26	12/6. 45	4.9	1.3	3.6	26.5	95						14.0	5.3	8.7	38.0
27	12/6. 45	6.4	1.8	4.6	28.1	124						6.3	4.3	2.0	68.3
Other chronic suppurative conditions:															
90	9/2. 46 27/3. 46 29/4. 46	5.9 5.2 5.3	3.5 3.0 3.1	2.4 2.2 2.2	59.3 57.5 58.5	363 262 195	213 156 86			59 60 44		4.1 3.3 2.3			
91	9/2. 46	3.9	1.9	2.0	48.7	320	205			64		6.9			
92	12/6. 46 17/6. 46	5.6	3.0	2.6	53.6	287 297	105 156	13.7 11.5	343 288	37 53	120 97	+	+		
93	11/3. 47 22/3. 47	6.5 7.4	2.8 3.1	3.7 4.3	43.1 41.9	228 248	140 150	14.0	350	61 61	154	3.2 3.9	1.5 3.8	1.7 0.1	46.9 97.4
94	11/3. 47 14 3. 47	5.4 5.6	1.4 1.9	4.0 3.7	24.1 33.9	281 230	160 121	13.1 16.8	328 420	57 53	116 183	8.9 12.9	1.4 11.5	4.0 1.4	15.7 89.1
Healthy control individuals (according to Helve):															
Mean (13)						177	105	9.3	233	59	131				
Lowest						113	66	7.4	186	43	76				
Highest						246	166	11.0	275	106	243				

¹ Date when the amyloid had evidently been resorbed.² Date when the amyloid had evidently not yet developed.

According to BING (1946) and his associates the relative albumin percentage is in normal individuals 56—76. The amyloid cases thus show marked changes in the ratio of albumin and globulin, the relative globulin level having increased. This is mainly due to the reduction of the serum albumin when excreted in the urine. In three examined cases (4, 8 and 27) the relative albumin level of the urine varied from 65 to 93.5 per cent. In one case (No 26), on the other hand the urinary globulin concentration was higher, while the relative albumin percentage was 38.

Case 1 was the one where no albumin occurred in the urine. At the time when this patient probably had amyloid in the organism, the protein fraction was carried out only in one examination. The relative albumin percentage was then 40. In the following four examinations, when the amyloid had evidently been resorbed, the corresponding level varied between 52 and 63.9 per cent. Contemporaneously with an increase of the albumin, reduction of the sedimentation rate on the blood could be noted. It is probable that the relative hyperglobulinaemia which was disclosed in the first examination was primarily due to the severe infection which had subsided considerably at the time of the following examinations. It is difficult to estimate to what extent the hyperglobulinaemia can be imputed to possible amyloidosis. In another severe case of empyema (No. 28, Table 12), where no amyloid was detected at autopsy, the relative protein percentage was almost identical. In Case 8 the albumin amount was larger in the first examination than in the examinations where albumin occurred in the urine and the condition could be established as amyloidosis.

Every one of the 5 *comparative cases* with amyloidosis (Nos. 90, 91, 92, 93 and 94) had albumin in the urine. No noteworthy divergencies were noted in these cases in the ratio of albumin and globulin compared with the cases of amyloidosis reviewed in the foregoing. In chronic cases of empyema of the pleura (Table 12) where no amyloid was detected the relative albumin percentage was higher than in the cases of amyloid nephrosis. Relative hyperglobulinaemia was evidently present in 4 out of 8 cases (2, 3, 7 and 28), whose relative albumin concentration was below 56 per cent.

As is evident from the foregoing, a reduction of the serum albumin and the total protein of the serum occurred in cases of amyloid degenera-

No.	Date of test	S e r u m				P l a s m a						
		Total protein %	Albumin %	Globulin %	Relative albumin %	C mg %	Ce mg %	Tlp mg %	P mg %	Ce/C %	P/C %	C.R.I.
2	8/9. 45	8.1				264						56
	14/9. 45											
	5/3. 46											
	16/4. 46											
	9/5. 46											
	20/6. 46	7.9	4.5	3.4	56.9	215	121	12.1	303	56	141	48
	19/9. 46	7.6	4.1	3.5	53.9	199	105	8.6	215	53	108	32
	11/12. 45	6.7	3.1	3.6	46.3	119	78			66		29
	29/4. 46	6.5	3.4	3.1	52.3							
	27/5. 46	7.1	4.4	2.7	62.0							
6	4/12. 46					312	172	12.0	300	55	96	40
	13/3. 46	7.4	4.9	2.5	66.2	144	72			50		38
7	26/4. 46	6.8	3.2	3.6	47.0	129	60			47		37
	9/5. 46	6.8	4.6	2.2	67.6	163	90			55		
	15/5. 46	6.6	4.5	2.1	68.1							
9	5/12. 46	6.8	4.6	2.2	67.6	285	171	22.0	550	60	193	35
10	9/11. 46	7.7	5.3	2.4	68.8	133	82	16.2	405	62	305	38
	3/12. 46	7.3	4.8	2.5	65.8							
28	14/9. 45	4.3	1.7	2.6	39.5	131						41
29	16/4. 46	6.7	4.2	2.5	62.7	203	111			55		53
39	25/5. 46					203	133	12.1	303	66	149	32

tion exhibiting albumin in the urine. The fall in the total proteins of the serum was primarily due to the severe albuminuria. My findings are thus in agreement with investigations carried out earlier in cases of nephrosis and amyloidnephrosis. In the single case of amyloidosis without urinary albumin hyperglobulinaemia was present, but not in more marked degree than in another suppurative case of equal severity.

Cholesterol and Lipid Phosphorus of Plasma

We can see from the survey of the literature that even markedly increased values of the total fatty acids and of the total cholesterol have occurred in cases of amyloid nephrosis as in other nephrotic conditions. The available literature, on the other hand, does not pay corresponding attention to phospholipids in cases of amyloid degeneration.

Of all the substances present in the blood the lipids show most conspicuous variation. BOYD (1935) stated that in healthy individuals the average daily fluctuation was to a marked extent dependent upon time, diet and rest. According to this author (1938) the plasma lipids contain normally, among other elements, 162 mg. per 100 cc. of total cholesterol, of which 115 mg. per 100 cc. is cholesterol ester, and 196 mg. per 100 cc. lipid phosphorus. SPERRY (1937) declared that the cholesterol level may normally rise as high as 250 mg. per 100 cc. VESA and T. KALAJA (1939) made corresponding determinations of the blood serum (by T. KALAJA's modified technique) in 16 cases, in which the obtained values varied from 169 to 286 mg. per 100 cc. HELVE (1947) carried out determinations of plasma lipids by the same method in 13 cases. The values for cholesterol and lipid phosphorus obtained by him in normal cases appear in Table 11.

My findings in cases of amyloidosis in connection with chronic empyema of the pleura are shown in Table 11. When comparing the levels of total cholesterol, cholesterol ester, total lipid phosphorus and total phosphatides with the normal values established by HELVE (1947) by means of the same method, only negligible differences are noted. I find these normal values suitable for use as a control material, since they were determined at the same laboratory and using the method applied in my investigations.

In Cases 4 and 5 the level of *total cholesterol* rose in comparison with the normal mentioned. In the former the lowest value in six examinations made in the course of approximately one year was 225 mg. per 100 cc., while the highest were 385, 438 and 461 mg. per 100 cc. In the latter case the corresponding value was 420 mg. per 100 cc. prior to death. The lowest total cholesterol concentrations 95 and 124 mg. per 100 cc. occurred in Cases 26 and 27, likewise ending fatally. It is possible that the patient's pre-mortal condition was of especial significance in causing this disorder. In Case 8, on the other hand, the total cholesterol amount was before amyloidosis 234 mg. per 100 cc., but after the development of evident amyloid degeneration 226 and 148 mg. per 100 cc.

Determinations of *cholesterol ester* were undertaken in Cases 4, 5 and 8. Case 4 showed elevated cholesterol ester values in the same examinations where high values were observed for total cholesterol. In Case 5 the relative value for cholesterol ester was markedly lowered, only 20 per cent. This points to an obstruction of the synthesis of ester and especially to a derangement of hepatic function. In the cholesterol amount of Case 8 we find nothing deserving special mention.

The concentration of *phospholipids* was slightly higher compared with normal cases. The amount of total lipid phosphorus varied in two examined cases (Nos. 4 and 8) from 10.5 to 14.8 mg. per 100 cc. and that of total phosphatides between 263 and 370 mg. per 100 cc. There were no marked changes in the ratio of phosphatides and total cholesterol in these cases. Case 8 had no fluctuation worth mentioning in the concentrations of phospholipids in those stages of the disease when amyloid had not yet developed.

The amyloid cases in the *comparative material* (Table 11; Cases 90—94) showed values which were in keeping with these findings. The amount of total cholesterol exceeded 300 mg. per 100 cc. in two cases (Nos. 90 and 91). In three examined cases (Nos. 92, 93 and 94) the values of the total lipid phosphorus rose in comparison with normal cases. The values varied between 11.5 and 16 mg. per 100 cc. in five examinations, the total phosphatide level being 288—420 mg. per 100 cc.

In cases of chronic empyema of the pleura (Table 12) the total cholesterol as well as cholesterol ester showed on an average lower concentrations than in amyloid disease. The values for phospholipids, on the other hand, were higher, which is in accordance with findings obtained in amyloid cases.

Summary

As a summary of investigations carried out in cases of amyloid degeneration which developed in connection with cases of chronic empyema of the pleura we may present the following:

Amyloid degeneration occurred in seven out of 59 cases. Five of these patients died and were subjected to autopsy, in one case the amyloid appeared to have been resorbed, and one patient still remained under treatment. Congo red tests were undertaken in all except one case. The clinical diagnosis was corroborated at autopsy in 4 cases and in one case the amyloidosis could not be established until autopsy. One of these cases revealed amyloid in the specimen obtained by liver puncture. In two cases the amyloidosis was diagnosed by means of the Congo red test only. The Congo red index was in these cases 77 and 75 per cent. Amyloidosis, in which all clinical symptoms usually indicative of amyloid were lacking, or in which in spite of occasional slight albuminuria no renal amyloid was disclosed at autopsy, occurred in 2 cases.

In four cases (and in addition in two comparative cases) where the diagnosis for amyloidosis could be confirmed by means of the liver puncture or at autopsy, the *Congo red index varied between 60 and 100 per cent*. Only one of these patients showed values below 60 per cent (56 and 57 per cent). The values obtained are in accord with those recorded by HARRISON (1947) et al.

In one case where the histological examination of the liver specimen did not reveal amyloid, amyloid degeneration could be established in the liver and in the kidneys at autopsy.

The shortest time in which amyloidosis was found to develop after the beginning of the suppuration was about 7 months. In the rest of the cases the suppuration had been continuing for from 1 to 2 ½ years before amyloidosis could be diagnosticated by means of the Congo red test. The period of suppuration before albumin was disclosed in the urine varied from 7 to 18 months. The bacterial variety, as was noted even by earlier investigators, did not seem to be of any importance in the development of amyloid. *In my cases, on the other hand, the persisting high temperature which accompanied suppuration seemed to promote the development of amyloidosis*.

Primarily due to severe albuminuria the serum albumin showed a decline. In 6 cases the relative albumin percentage ranged from 26.5

to 52. One of four examined patients exhibited a larger urinary excretion of globulin than albumin, the percentage of which was 38. The findings for cases of amyloid nephrosis were thus in agreement with data submitted by several earlier investigators. One patient with amyloidosis who had no albumin in the urine exhibited relative hyperglobulinaemia. However, this was not of a more striking type than that occurring in another case of severe suppurative infection, where no amyloid was revealed at autopsy.

The amounts of different lipid substances varied considerably. Besides fully normal total cholesterol concentrations other either slightly reduced or increased values could occur, as has been shown by earlier authors. In two cases the total cholesterol amount was low (95 and 124 mg. per 100 cc.) prior to death. One patient, on the other hand, showed a slightly increased total cholesterol content before death (420 mg. per 100 cc.), but the relative cholesterol ester was only 20 per cent. The reduction in cholesterol ester is indicative of derangement of hepatic function. In addition, evident hypercholesterolaemia (461 mg. per 100 cc.) was present in another case. In two cases the values were normal.

The phospholipids (total lipid phosphorus and phosphatides) had increased in two examined cases, likewise in three amyloid cases in the comparative material.

My material is too meagre to justify reliable conclusions on lipid metabolism in amyloid cases. The rôle played by lipids in amyloid degeneration seems to be of variable character and difficult to explain.¹

¹ I refer to a paper read by me at the meeting of the Association of Finnish Surgeons on Plasma Proteins and Cholesterol in Amyloid Degeneration. Rev. in Nord. Med. 1947;35:1602.

SUMMARY

The object of this investigation was to shed light upon aspects of metabolism in cases of chronic, especially non-specific cases of empyema of the pleura. With a view to this I carried out studies of protein, chloride and acid-base balance and determinations of the blood sugar content. The vitamin C of the serum was determined, in addition. Especial attention was paid to metabolism in amyloid disease.

The material comprised 59 cases in all of chronic empyema of the pleura, who were under clinical treatment at the Department for Chest Surgery connected with the Second Surgical University Clinic, Helsinki. The majority of the patients were soldiers in whom the disease had developed in consequence of war wounds in the chest. 44 were traumatic cases of chronic empyema and 15 non-traumatic. Six of the latter were tuberculous, seven metapneumonic, and in two cases the chronic empyema had developed as a sequel to pleuritis. Four patients, in addition, had developed tuberculosis as a complication of traumatic empyema.

The material with which the chronic cases of empyema of the pleura were compared consisted of 23 chronic cases of pulmonary disease and 7 cases of acute suppurative pleuritis. Comparative examinations were made in 5 patients with amyloidosis, whose primary disease was not chronic pleuritis. Studies of physiological changes were carried out in 5 indifferent sick-cases in the course of 6 days. The number of healthy control subjects was 28.

The values obtained on healthy control subjects were in agreement with the normal values recorded in the literature. The serum proteins, the serum chlorides and the alkali reserve showed only

slight physiological changes. Stasis was found to cause variation in the consistence of the serum.

On the basis of my findings I would submit the following answers to the questions raised at the beginning of this work (Pages 12 and 13):

1. *In chronic cases of empyema of the pleura without amyloid nephrosis the serum protein level was normal before operations performed, though in certain cases low values which yet remained within normal limits were obtained. Hypoproteinemia (below 6 per cent) occurred only, besides immediately after operation, in cases of amyloid nephrosis and in some severe suppurative conditions following operations as late as after 5—7 weeks. The lowest level was observed in conditions with extremely severe suppuration, at the terminal stage of the disease.*

2. *Quite considerable variation could occur in the serum chloride concentration in chronic empyema of the pleura. Along with normal values evident hypochloraemia (below 560 mg. NaCl per 100 cc.), was noted in several cases, exclusive of those cases of hypochloraemia which were due to a possible rise of temperature, operation or tuberculosis. In cases where a suppurating fistula led into the empyema cavity the hypochloraemia noted was not of such grave type as after operations when there was a severe wound infection. Thus, in prolonged suppurative conditions following operations undertaken to obliterate the cavity, hypochloraemia of different stages could be noted still after about 1—6 weeks. The lowest concentrations (below 500 mg. per 100 cc.) occurred in association with extremely severe wound infections at the terminal stage of the disease.*

3. *The amount of the alkali reserve was normal in the chronic cases of pleural empyema. The cases where a suppurating fistula led into the empyema cavity showed no noteworthy differences in comparison with suppurative conditions following various operations. Yet in some cases where investigations were made in the course of a whole year, increase of the alkali reserve level within normal limits seemed to occur along with an improvement of the general condition and while the wound was healing. When the general condition declined the alkali reserve showed reduction. Before death an evident decline of the alkali reserve within normal limits was observable, a shift of the acid-base balance of the organism in the acid direction («pre-mortal acidosis»).*

4. The fasting values of the blood sugar were normal in the 24 cases examined. In agreement with findings recorded in the literature, obtained in other infectious diseases, the chronic cases of empyema of the pleura which were examined by me seemed to exhibit changes after the intake of glucose which pointed to a decline in the carbohydrate tolerance.

5. Reduction was noted in several cases in the vitamin C concentration of the serum compared with normal cases. In cases where the examinations could be made before the patients had taken vitamin C, evident seasonal changes were observed. The vitamin C deficiency of the organism seemed to be greater, on an average, in the spring and in early summer than in the winter and in the autumn. The lowest vitamin C values (zero values) occurred prior to death in connection with extremely severe wound infections.

6. Amyloid degeneration seems to be one of the most severe complications of patients suffering from chronic empyema of the pleura. Among 59 chronic cases amyloidosis developed in seven chronic cases of empyema. (The investigation material contains the severest cases out of a great number that were sent from different parts of the country to the Hospital for Chest Injuries. A good many of them had been suffering from the disease for several years before they were admitted at the Hospital.) Five of these patients died and were subjected to autopsy, the treatment of one still continues, and in one case the amyloid has evidently been resorbed. Two patients exhibited amyloidosis with no observable clinical symptoms.

As regards the development of amyloidosis in my material, the length of the suppurative period did not seem to be of any decisive importance. The shortest period of suppuration during which amyloidosis developed was about 7 months. On the other hand, a prolonged fever concurrent with suppuration appeared to promote the development of amyloid in my cases.

BENNHOLD'S Congo red test seemed to be a valuable diagnostic medium for establishing amyloidosis in chronic cases of empyema of the pleura. In all cases where the disappearance of the dye from the blood was 60 per cent or more within 1 hour, amyloid degeneration could be established at autopsy or by means of a liver puncture. Yet one amyloid case showed values falling below this limit.

Primarily due to severe albuminuria reduction was noted in the albumin level of the serum.

The ratio of lipids in amyloid degeneration is a matter which is open to some question. Along with fully normal cholesterol amounts slightly lowered or increased values could be observed. In the cases of amyloid nephrosis as generally in nephrotic conditions the phospholipids showed increase. No special ratio could be established for the fluctuations of lipids and proteins.

REFERENCES

- AALKJÆR, V.: Væskeforholdene ved kirurgiske Sygdomme. Ejnar Munksgaard. København. 1943.
- AALTO, J. S.: Studies of Cardiac Disturbances in Cases of Healed Traumatic Chronic Empyema of the Pleura. — *Ann. Chir. Fenn.* 1947. Suppl. 2.
- ABBASY, M. A., HARRIS, L. J. and HILL, G.: Vitamin C and Infection. — *Lancet.* 1937:2:177.
- ALDER, A.: Anhaltspunkte für die Prognosenstellung der Lungentuberkulose aus refraktometrischen und viskosimetrischen Serumuntersuchungen. — *Z. Tbk.* 1919:31:10.
- ANDERSEN, J. and SCHMIDT, A.: Zur Frage des Blutzuckerspiegels bei Infektionskrankheiten. — *Klin. Wschr.* 1927:5:213.
- ANTONIN, V.: Einfluss der Lokal- und Lumbalanästhesie auf den acidobasischen Haushalt in der postoperativen Zeit und die Bedeutung der Vorbereitung des Kranken auf diese Verhältnisse. — *Acta Chir. Scand.* 1931:66:78.
- APITZ, K.: Die Paraproteinasen. Über die Störung des Eiweisstoffwechsels bei Plasmocytom. — *Virchows Arch.* 1940:306:631.
- AREY, L. B.: Wound Healing. — *Physiol. Rev.* 1936:16:327.
- BANG, I.: Ein Verfahren zur Mikrobestimmung von Blutbestandteilen. — *Biochem. Z.* 1913:49:19.
- BARBOUR, H. C. and HAMILTON, W. F.: Heat Regulation and Water Exchange. — *Amer. J. Physiol.* 1925:73:315.
- BARTLETT, M. K., JONES, C. M. and RYAN, A. E.: Vitamin Studies on Surgical Patients. — *Ann. Surg.* 1940:111:1.
- BEATTIE, J. M. and DICKSON, W. E. C.: A Textbook of Pathology General and Special. William Heinemann Ltd. London. 1943.
- BEAUMONT, G. E. and DODDS, E. C.: Recent Advances in Medicine. J. and A. Churchill Ltd. London. 1944.
- BECHER, E., ENGER, R. and HERRMANN, E.: Die ätherlöslichen Säuren des Blutes bei der urämischen Acidose. — *Klin. Wschr.* 1932:11:891.
- BENNET, M. A.: Some Changes in the Acid-Base Equilibrium of the Blood Caused by Hemorrhage. — *J. Biol. Chem.* 1926:69:675.
- BENNHOLD, H.: Über die Ausscheidung intravenös einverleibten Kongorotes bei den verschiedensten Erkrankungen, insbesondere bei Amyloidosis. — *Dtsch. Arch. klin. Med.* 1923:142:32.

- BENNHOLD, H.: Über die Beziehungen des Kongorotes zur amyloiden Substanz und über den Mechanismus der Beschleunigten Farbstoffausscheidung bei tubulären Nierenkrankheiten. — *Klin. Wschr.* 1924:38:1711.
- BERG, S.: Till frågan om sockeromsättningen vid tuberkulos. — *Sv. Läkartidn.* 1924:21:874.
- BERG, S.: Contribution to the Question of Sugar Metabolism in Pulmonary Tuberculosis. — *Acta Med. Scand.* 1932:78:66.
- BERGER, W.: Über die Hyperproteinämie nach Eiweissinjektionen. — *Z. exper. Med.* 1922:28:1.
- BEST, C. H. and TAYLOR, N. B.: *The Physiological Basis of Medical Practice.* Ballière, Tindall and Co. London. 1945.
- BIERNACKI, E.: Untersuchungen über die chemische Blutbeschaffenheit bei pathologischen, insbesondere bei anämischen Zuständen. — *Z. Klin. Med.* 1894:24:460.
- BING, J., NAESER, J., RASCH, C. and RØJEL, K.: Serum Proteins in Normal People. — *Acta Med. Scand.* 1946:126:351.
- BJÖRNEBOE, M. and GORMSEN, H.: Kemiske og histologiske Undersøgelser over Antistofdannelsen. — *Nord. Med.* 1943:79:1155.
- BLIX, G., TISELIUS, A. and SVENSSON, H.: Lipids and Polysaccharides in Electrophoretically Separated Blood Serum Proteins. — *J. Biol. Chem.* 1941:137:485.
- BLOOR, W. R.: A Method for Determination of Fat in Small Amounts of Blood. — *J. Biol. Chem.* 1914:17:377.
- BLUM, L., GRABAR, P. and VAN CAULAERT: L'azotémie par manque de sel. — *Presse méd.* 1928:28:1411.
- BODANSKY, M. and BODANSKY, O.: *Biochemistry of Disease.* The Macmillan Co. New York. 1944.
- BOENHEIM, F.: Der Chlorgehalt des Blutes und Serums unter physiologischen und der verdauungspathologischen Umständen. — *Z. exper. Med.* 1921:12:295.
- BOENHEIM, F.: Der Chlorstoffwechsel bei Lungentuberkulose. — *Beitr. Klin. Tbk.* 1922:49:233.
- BOHMANSSON, G.: Acidosis och alkalosis och deras behandling vid kirurgiska sjukdomar. — *Nord. Med.* 1943:20:1817.
- BOHMANSSON, G.: Blodäggvitans betydelse vid kirurgiska sjukdomar. — *Nord. Med.* 1944:21:127.
- BOOKMAN, A. and ROSENTHAL, J.: The Clinical Value of Intravenous Injections of Congo Red in the Diagnosis of Amyloid Disease. — *Amer. J. Med. Sci.* 1927:173:396.
- BOYD, E. M.: Diurnal Variations in Plasma Lipids. — *J. Biol. Chem.* 1935:110:61.
- BOYD, E. M.: Quoted by WUNDERLY.
- BREMS, A.: Störungen des Kohlehydratstoffwechsels bei Diabetikern. — *Klin. Wschr.* 1932:895.

- BREMS, A. and NISSEN, A. J.: On Perorale og enkelte intravenøse Glukose-belastningskurven ved visse akute Infektionssygdomme. — Ugeskr. Laeg. 1932:94:1203.
- BRENNAN, H. J.: Plasma Transfusions in the Treatment of Haemorrhage. — Brit. Med. J. 1940:1:1047.
- BRIGGS, A. P.: A Study of the Inorganic Elements of the Blood Plasma. — J. Biol. Chem. 1923:57:351.
- BRØCHNER-MORTENSEN, K.: Hypoproteinemia in Chronic Pemphigus. — Acta Med. Scand. 1938:97:329.
- BØGGILD, D.: Tilfælde af Acidose ved Peritonitis behandlet med Bikarbonatopløsning. — Ugesk. Læger. 1942:104:1116.
- BÖHME, A.: Über die Schwankungen der Serumkonzentration beim Gesunden Menschen. — Dtsch. Arch. klin. Med. 1911:103:522.
- CARR, J.: Laboratory Routine for Fluid Electrolyte and Protein Control in Surgical Patients. — Surg. etc. 1944:79:438.
- CHASSIN, A. and SCHAPIRO, A.: Über den Einfluss der operativen Eingriffe auf den Kohlenhydratumsatz und das Säurebasengleichgewicht. — Arch. klin. Chir. 1928:153:335.
- CHRISTENSEN, S.: Undersøgelser over Clorionernes Forhold i Blodet ved Otitis media suppurativa acuta. — Hosp. tid. 1938:81:1107.
- COLLER, F. A., DICK, V. S. and MADDOCK, W.: Maintenance of Normal Water Exchange with Intravenous Fluids. — J. Amer. Med. Assoc. 1936:107:1522.
- CONRAD, H.: Untersuchungen über den Vitamin B- und Vitamin C-Stoffwechsel bei chronisch eiternden Wunden. — Münch. med. Wschr. 1944:91:31.
- CRECELIUS, W.: Gefahrdrohende Senkung des Blutzuckerspiegels beim Diabetiker während einer interkurrenten fieberhaften Erkrankung. — Dtsch. med. Wschr. 1929:25:1040.
- DAGULF, H.: Ascorbinsäurestudien an Gesunden und Tuberkulosekranken. — Diss. Lund. 1939.
- DAUTREBONDE, L., DAVIES, H. W. and MEAKINS, J.: The Influence of Circulatory Changes on the Gaseous Exchanges of the Blood. — Heart. 1923:10:133. Quoted by PETERS and VAN SLYKE.
- DIECKHOFF, J.: Stoffwechseluntersuchungen bei Diphtherie. — Z. exper. Med. 1939:105:607.
- DIECKHOFF, J.: Über Störungen des Mineralstoffwechsels und der Capillarpermeabilität bei schweren Infektionskrankheiten bzw. experimenteller Diphtherie- und Dysenterieintoxikation. — Klin. Wschr. 1943:22:378.
- DIECKHOFF, J. and SCHÜLER, K.: Zur Behandlung der toxischen Diphtherie mit C-Vitamin und Nebennierenrindenhormon. — Klin. Wschr. 1938:17:936.
- DIFS, H.: Beiträge zur Diagnostik der Vitamin C-Mangelkrankheit. — Acta Med. Scand. 1940. Suppl. 110.

- DILL, D. B.: Life, Heat and Altitude. Cambridge, Harvard University Press 1938. Quoted by KØSTER and TROLLE.
- DODDS, E. C. and SMITH, K. S.: Variations in the Blood Chlorides in Relation to Meals. — *J. Physiol.* 1924:58:157.
- DRAGSTEDT, L. R.: The Effect of Streptococcus Hemolyticus Infection on the Reaction of the Blood of Rabbits. — *J. Infect. Dis.* 1920:27:452.
- EHRSTRÖM, M. CH.: Om förändrade fysikaliska egenskaper hos plasmaproteinerna vid nefros. — *Finska Läk. sällsk. Hdl.* 1936:79:541, 802.
- EICHELBERGER, L. and MCCLUSKEY, K. L.: Chemical Studies in Tuberculosis. — *Arch. Int. Med.* 1927:40:831.
- EITEL, H. and TRÜCK, W.: Die Bedeutung des antiskorbutischen Vitamins für die Behandlung chirurgischer Erkrankungen. — *Arch. Klin. Chir.* 1937:190:307.
- EKLUND, C. M. and REIMANN, H. A.: Etiology of Amyloid Disease, with Note on Experimental Renal Amyloidosis. — *Arch. Path.* 1936:21:1.
- EPPINGER, H.: Die seröse Entzündung. Julius Springer. Wien. 1935.
- ESSEN, H., KAUDERS, F. and PORGES, O.: Die Beziehungen der CO₂-Spannung der Alveolarluft zu den Chloriden des Blutserums. — *Wien. Arch. inn. Med.* 1923:5:499.
- FARMER, C. J. and ABT, A. F.: Ascorbic Acid Content of Blood. — *Proc. Soc. Exper. Biol. a. Med.* 1935:32:1625.
- FETZER, H. C.: Untersuchungen über die Beziehungen zwischen Kohlehydratstoffwechsel und experimenteller Staphylokokkeninfektion beim Kaninchen. — *Arch. Hyg.* 1932:107:225.
- FISKE, C. H. and SUBBAROW, Y.: The Colorimetric Determination of Phosphorus. — *J. Biol. Chem.* 1925:66:375.
- FLEISCHHACKER, H.: Über die Plasmazellen und des reticuloendotheliale System des Knochenmarkes. — *Dtsch. Arch. klin. Med.* 1940:186:506.
- FLETCHER, A.: Dietetic Treatment of Chronic Arthritis and its Relationship to the Sugar Tolerance. — *Arch. Int. Med.* 1922:30:106.
- FOLEY, E., KEETON, R., KENDRICK, A. and DARLING, D.: Alterations of Serum Protein as an Index of Hepatic Failure. — *Arch. Int. Med.* 1937:60:64.
- FOLIN, H. and WU, H.: A System of Blood Analysis. — *J. Biol. Chem.* 1919:38:81.
- FORSSELL, J.: Morphologische Veränderungen in Knochenmark und Blut bei akuten Blutungsanämien. — *Diss. Helsingfors.* 1939.
- FORSTER, E.: Die Rolle des C-Vitamins in der Chirurgie. — *Helvet. med. Acta.* 1937:4:676.
- FRASER, ALBRIGHT and SMITH: Quoted by BEAUMONT and DODDS.
- GAESSLER, E. O.: Blutmilchsäure Alkalireserve und Blutzucker in ihrer Bedeutung für Diagnose, Therapie und Prognose puerperaler Infektion. — *Klin. Wschr.* 1930:9:1222.
- GAMBLE, J. L., ROSS, S. G. and TISDALL, F. F.: The Metabolism of Fixed Base during Fasting. — *J. Biol. Chem.* 1923:57:633.

- GARDNER, W.: Trans. Assoc. Amer. Physicians 1891:6:149. Quoted by PEARLMAN.
- V. GIERKE, E.: Störungen des Stoffwechsels. — ASCHOFF, L.: Pathologische Anatomie. Gustav Fischer. Jena. 1936. Volume 1:326.
- GRAYZELL, H. G. and JACOBI, M.: Secondary Amyloidosis: Results of Therapy with Desiccated Whole Liver Powder. — Ann. Int. Med. 1938:12:39.
- GREENWALD, G. K. and HARDE, E.: Vitamin C and Diphteria Toxin. — Proc. Soc. Exper. Biol. a. Med. 1935:32:1157.
- GREENWALD, I.: Studies in Metabolism in Pneumonia. — Arch. Int. Med. 1931:48:418, 440.
- GROTH-PETERSEN, B. and GROTH-PETERSEN, E.: C-Vitaminet og Tuberkulose. — Nord. Med. 1939:2:1565.
- HABEIN, H. C.: Proc. Stoff Meet. Mayo Clinic. 1934:9:261. Quoted by PEARLMAN.
- HACHEN, D. S.: The Alkali Reserve in Pulmonary Tuberculosis. — Arch. Int. Med. 1922:29:705.
- HACHEN, D. S. and ISAACS, R.: The Alkali Reserve in Epidemic Influenza and Bronchopneumonia. — J. Amer. Med. Assoc. 1920:75:1624.
- HAGEDORN, H. C.: Undersøgelser vedrørende Blodsukkerregulationen hos Mennesket. København. 1921.
- HAGEDORN, H. C. und JENSEN, B. N.: Zur Mikrobestimmung des Blutzuckers mittels Ferricyanid. — Biochem. Z. 1923:135:46 and 137:92.
- HARRISON, G. A.: Chemical Methods in Clinical Medicine. J. and A. Churchill Ltd. London. 1947.
- HARTMANN, A. F., PERLEY, A. M., BOSMANN, J., NELSON, M. and ASHER, C.: Further Observations on the Metabolism and the Clinical Uses of Sodium Lactate. — J. Pediatr. 1938:13:692.
- HASSELBACH, F.: Das Vitamin C-Defizit bei Tuberkulösen. — Dtsch. med. Wschr. 1936:23:924.
- HASSELBACH, F.: Die Rolle der Vitamine bei der Behandlung der Tuberkulose. — Klin. Wschr. 1937:16:472.
- HASTINGS, A. B., NEILL, J. M., MORGAN, H. J. and BINGER, C. A. L.: Blood Reaction and Blood Gases in Pneumonia. — J. Clin. Invest. 1924:1:25.
- HAUSBERGER, F. X. and NEUENSCHWANDER-LEMMER, N.: Beziehungen zwischen Vitamin C Blutspiegel und Fieberstoffwechsel. — Klin. Wschr. 1939:18:1119.
- HAWK, P. B., OSER, B. L. and SUMMERSON, W. H.: Practical Physiological Chemistry. The Blakiston Co. Philadelphia and Toronto. 1947.
- HEILMEYER, L.: Die Natrium-Chlor-Regulation. — Dtsch. Arch. klin. Med. 1927:156:200.
- HELVE, O.: A Study of the Metabolism in Addison's Disease. II. — Acta Med. Scand. 1947:128:1.
- HENRIQUES, V. and KLAUSEN, U.: Untersuchungen über den Serumalbumin- und Serumglobulingehalt des Serums unter wechselnden Umständen. — Biochem. Z. 1932:254:414.

- HERLITZ, C. W.: Investigations of the C-Vitamin Standard in Healthy Children and in Children Suffering from Gingivitis. — *Acta Paediatr.* 1938:23:43.
- HERRMANNSDORFER, A.: Über den Einfluss der Nahrung auf die Pufferkapazität des Blutes und den Heilverlauf und den Keimgehalt granulierenden Wunden. — *Dtsch. Z. Chir.* 1927:200:534.
- HIMSWORTH: Quoted by BEAUMONT and DODDS.
- HIRSCH, E. F.: Changes in Leucocytes and Alkali Reserve of Blood in Experimental Infections. — *J. Infect. Dis.* 1921:28:275.
- HIRSCH, E. F.: Changes in the Alkali Reserve, Sugar Concentration, and Leucocytes of the Blood in Experimental Infections. — *J. Infect. Dis.* 1921:29:40.
- HJÄRNE, U.: A Study of Orthoglycaemic Glycosuria with Particular Reference to its Heritability. — *Acta Med. Scand.* 1927:47:422.
- HJÄRRE, A.: Om amyloidoser med särskild hänsyn till förhållandena hos djuren. — *Nord. Med.* 1945:26:1099.
- HOLSTI, Ö.: Om förekomsten och betydelsen av abnorma blodsockerreaktioner vid reumatisk artrit. — *Finska Läk. sällsk. Hdl.* 1924:66:217.
- HOLSTI, Ö.: Om blodsockerreaktionens variationer vid ett antal sjukdomar. — *Finska Läk. sällsk. Hdl.* 1926:68:549.
- HOLTEN, C.: The Formation of Organic Acids and the Retention of Chlorides in Lobar Pneumonia. — *Arch. Int. Med.* 1926:38:489.
- HOOVER, C. F. and TAYLOR, L.: The Ventilatory Function of the Lung in Emphysema and Asthma. — *Arch. Int. Med.* 1915:15:1.
- HORELLI, V.: C-vitamiini ja keuhkotuberkuloosi. — *Duodecim.* 1937:53:1111.
- HUNT, A. H.: The Role of Vitamin C in Wound Healing. — *Brit. J. Surg.* 1941:28:436.
- HÜSCH, L.: Kohlenhydratstoffwechsel und Glykosurie bei akuten fieberhaften Erkrankungen. — *Münch. med. Wschr.* 1936:83:1467.
- HÖGLER, F. and ÜBERROCK, K.: Über den Wasser- und Salzstoffwechsel nach Schwitzen. — *Wien. Arch. inn. Med.* 1927:13:465.
- IPSEN, J.: Serum-Clor-Maalingersbetydning for den croupøse Pneumonis Prognose og Behandling. — *Ugeskr. Læg.* 1936:98:1161.
- JAFFÉ, R. H.: *Arch. Path. a Labor. Med.* 1926:2:149. Quoted by LETTERER (1934).
- JENSEN, O.: Om syre-baselikevekten og elektrolyttene i blodet. Tanum. Oslo. 1942.
- JOHANSSON, G. A.: Amyloidosens klinik. — *Nord. Med.* 1945:26:1102.
- JOHANSSON, G. A.: Plasmaäggvitan och plasmalipoiderna vid amyloidnefroser. — *Nord. Med.* 1946:31:2007.
- JOSEFSON: Quoted by WALDENSTRÖM.
- JUSATZ, J. H.: Über den Einfluss von Vitamin C auf Immunitätsvorgänge. — *Z. Vitaminforsch.* 1939:9:75.
- KALAJA, L.: Über Hypochlorämie. — *Acta Soc. Medic. Fenn. Duodecim. Ser. B. Tom. XXXI. Fasc. 2.* 1945.

- KALAJA, T. and HELVE, O.: On Plasma Lipids in Certain Internal Diseases. — *Ann. Med. Fenn.* 1947:36:66.
- KAUDERS, F. and PORGES, O.: Über die Beziehungen der Kohlensäurespannung der Alveolarluft zur Pathologie der Magensaftsekretion. — *Wien. Arch. inn. Med.* 1923:5:379.
- KEITH, N. M., ROWNTREE, L. G. and GERAGHTY, J. T.: A Method for the Determination of Plasma and Blood Volume. — *Arch. Int. Med.* 1915:16:547.
- KINGSLEY, G. R.: The Determination of Serum Total Protein, Albumin and Globulin by the Biuret Reaction. — *J. Biol. Chem.* 1939:131:197.
- KINGSLEY, G. R.: A Rapid Method for the Separation of Serum Albumin and Globulin. — *J. Biol. Chem.* 1940:133:731.
- KIRK, E.: Der Wasser- und Salzhaushalt des Körpers unter normalen und pathologischen Verhältnissen. — *Dtsch. med. Wschr.* 1939:65:1741.
- KIRK, E.: Klinik und Behandlung der Acidose. Ejnar Munksgaard. København. 1944.
- KIVIMÄKI, J.: Über die C-Vitaminlage beim finnischen Volke. — *Acta Odont. Scand.* 1940:2:53.
- KOEHLER, A. E.: Acid-Base Equilibrium. I. Clinical Studies in Alkalosis. — *Arch. Int. Med.* 1923:31:590. Quoted by PETERS and VAN SLYKE.
- KOREF, O.: Klinische Analyse einer Amyloidose. — *Med. Klin.* 1924:20:1243.
- KRETZSCHMAR, P. H. and WESTBROOK, B. P.: *Proc. Soc. Med. County Kings.* 1880:5:343. Quoted by PEARLMAN.
- KROGH, A.: The Anatomy and Physiology of Capillaries. New Haven. 1922. Quoted by LANGE.
- KUCZYNSKI, M. H.: Neue Beiträge zur Lehre vom Amyloid. — *Klin. Wschr.* 1923:2:727, 2193.
- KÖSTER, K. H. and TROLLE, D.: Investigations of Postoperative Shock: Haemoconcentration, Plasma Protein and Blood Electrolytes after Gastrectomy. — *Acta Chir. Scand.* 1946:93:51.
- LANGE, H. F.: The Normal Plasma Protein Values and Their Relative Variations. — *Acta Med. Scand.* 1946. Suppl. 176.
- LAUBER, H. J., BERSIN, TH. and NAFZIGER, H.: Der Einfluss von Narkose und Operation auf den Vitamin C-Haushalt. — *Klin. Wschr.* 1937:16:1272.
- LAUBER, H. J., BERSIN, TH. and NAFZIGER, H.: Der Ascorbinsäurebedarf bei chirurgischen Infektionen. — *Klin. Wschr.* 1937:16:1274.
- LAURENT, B. and LAMBERG, A.: Om biuretreaktionen. — *Nord. Med.* 1947:35:1795.
- LAUTROP, H. and MADSEN, H.: Nogle undersøgelser over hypokloræmi og hypokloruri ved infektionssygdomme med diskussion af tilhørende problemer. — *Nord. Med.* 1942:13:321.
- LAWRENCE, R. D. and McCANCE, R. A.: Infections and Insulin Action. — *Brit. Med. J.* 1931:1:749.

- LEHMANN, J.: Laboratorieanalyser nödvändiga för kontroll av vätske-, salt- och proteinbehandling. — Nord. Med. 1944:21:317.
- LEHMANN, J.: Om tarmperistaltikens förhållande till koksalthalten i blod och urin. — Nord. Med. 1944:21:410.
- LEPPO, E.: A- ja C-vitamiinien merkityksestä infektio-tauteissa. — Duodecim. 1939:55:129.
- LETTERER, E.: Experimentelle Studien über Art und Entstehung des Amyloids. — Zbl. inn. Med. 1926:47:417.
- LETTERER, E.: Neue Untersuchungen über die Entstehung des Amyloids. — Virchows Arch. 1934:293:34.
- LICHTENSTEIN, L. and EPSTEIN, E. Z.: The Blood Lipoids in Nephrosis and Chronic Nephritis with Edema. — Arch. Int. Med. 1931:47:122.
- LICHTWITZ: Handbuch d. inneren Medizin von Mohr—Staehelin. 1927. Bd. 4. S. 729. Quoted by SICK.
- LIPSTEIN, S.: An Evaluation of the Congo-Red Test for Amyloidosis. A Correlation of the Autopsy Findings and Dye Absorption in 125 Cases. — Amer. J. Med. Sci. 1938:195:205.
- LOESCHKE, H.: Vorstellungen über das Wesen von Hyalin und Amyloid auf Grund von serologischen Versuchen. — Beitr. path. Anat. 1927:77:231.
- LOHMANN, K. and JENDRASSIK, L.: Kolorimetrische Phosphorsäurebestimmungen im Muskelextrat. — Biochem. Z. 1926:178:419.
- LUFT, R.: Quoted by Nord. Med. 1946:29:93.
- LUND, H. and LIECK, H.: Quantitative Bestimmung von Ascorbinsäure im Blutserum. — Klin. Wschr. 1937:16:555.
- LUNDGAARD, C.: Studies on Cyanosis. — J. Exper. Med. 1919:30:259.
- LÜTHY, F.: Klinische Untersuchungen über Serumeiweisskörper bei Lungentuberkulose. — Schweiz. med. Wschr. 1927:42:993.
- LÖHR, W.: Wundheilung. Johann Ambrosius Barth. Leipzig, 1937.
- MACLEAN, A. B. and SULLIVAN, R. C.: Dextrose Tolerance in Infants and in Young Children. — Amer. J. Dis. Childr. 1929:37:1146.
- MALMROS, H.: A Study of Glucosuria with Special Reference to the Interpretation of the Incidental Finding of a Positive Reduction Test. — Acta Med. Scand. 1928. Suppl. 27.
- MARBLE, A.: Cause of Lowered Tolerance for Carbohydrate during an Infection. — JOSLIN, E. P.: Treatment of Diabetes Mellitus. Henry Kimpton. London. 1946.
- MAURIAC, P.: Oedème et suppuration pleurale tuberculeuse. — Presse méd. 1936:44:1215.
- MCCANCE, R. A.: Medical Problems in Mineral Metabolism. — Lancet. 1936:1:823.
- MCLEAN, F. C.: The Numerical Laws Governing the Rate of Excretion of Urea and Chlorides in Man. — J. Exper. Med. 1915:22:366.
- MEAKINS, J. C. and DAVIES, H. W.: Observation on the Gases in Human Arterial and Venous Blood. — J. Path. a. Bacter. 1920:23:451.

- MELZER, E.: Über die Grösse des Vitamin C-Defizitis und seine therapeutische Bedeutung bei Lungentuberkulose. — Dtsch. Tbk.bl. 1938: 12:290.
- MENTEN, M. L. and CRILE, G. W.: Studies on the Hydrogen-Ion Concentration in Blood under Various Abnormal Conditions. — Amer. J. Physiol. 1915:38:225.
- MILAM, D. F. and DURHAM, N. C.: Plasma Protein Levels in Normal Individuals. — J. Labor. a. Clin. Med. 1946:31:285.
- MYERS, W. and KEEFER, C.: Relation of Plasma Proteins to Ascites and Edema in Cirrhosis of the Liver. — Arch. Int. Med. 1935:55:349.
- MÜLLER, P. und ANTHES, H.: Untersuchungen über den Stoffwechsel bei Tuberkulose. — Arch. klin. Med. 1927:158:54.
- MÜLLER, P. und QUINCKE, H.: Untersuchungen über den Stoffwechsel bei Tuberkulose. — Arch. klin. Med. 1927:158:42, 62.
- NATHAN, M.: Über die klinische Diagnose der Amyloidose mittels Kongorotinjektionen. — Münch. med. Wschr. 1928:75:1883.
- NÉMETH, L.: Über den klinischen Wert des Nachweises der Amyloidose durch die Kongorotprobe. — Klin. Wschr. 1926:5:1040.
- NILSSON, P.: Om C-vitaminhalten i blodserum vid olika psykosformer och dess förändring vid belastning. — Nord. Med. 1939:1:600.
- NIOSI, G. S.: Degenerazione amiloide a splenectomia. — Pathologica. 1937:29:155.
- NOWAK, J.: Experimentelle Untersuchungen über die Ätiologie der Amyloidosis. — Virchows Arch. 1898:152:162.
- NYLANDER, P. E. A.: Über den Einfluss der A- und C-Avitaminose auf die Reaktionsfähigkeit des Peritonealgewebes. — Acta Soc. Medic. Fenn. Duodecim. Ser. A. Tom. XXII. Fasc. 1. 1940.
- ODIN, M.: C-Vitaminstandard und C-Hypovitaminose. — Acta Paediatr. 1939:26:339.
- PAINE, J. R. and ARMSTRONG, W. D.: A Study of Fluid and Sodium Chloride Balance in Patients Treated with Continuous Suction Applied to Indwelling Duodenal Tubes. — Surg. etc. 1939:68:751.
- PALMER, W. W. and HENDERSON, L. J.: A Study of Several Factors of Acid Excretion in Nephritis. — Arch. Int; Med. 1915:16:109.
- PARSON, T., PARSON, W. and BARCROFT, J.: Reaction Changes in the Blood during Muscular Work. — J. Physiol. 1920:53:110.
- PAUNZ: Quoted by NÉMETH.
- PEABODY, E. W.: Studies in the Inorganic Metabolism in Pneumonia with Especial Reference to Calcium and Magnesium. — J. Exper. Med. 1913: 17:71.
- PEARLMAN, A. W.: Regression of Amyloidosis. — Quart. Bull. Sea View Hosp. 1940:6:82.
- PEMBERTON, R.: Studies on Arthritis in the Army Based on Four Hundred Cases. — Arch. Int. Med. Febr. and March 1920. Quoted by HOLSTI.
- PERÄSALO, O.: On Plasma Proteins and Cholesterol in Amyloid Degeneration. — Nord. Med. 1947:35:1602.

- PETERS, J. P., BULGER, H. A., EISENMAN, A. J. and LEE, C.: Total Acid-Base Equilibrium of Plasma in Health and Disease. — *J. Biol. Chem.* 1926:67:141, 159, 175, 219.
- PETERS, J. P., EISENMAN, A. J. and BULGER, H. A.: The Plasma Proteins in Relation to Blood Hydration. — *J. Clin. Invest.* 1925:1:435.
- PETER and GYELIN: Quoted by HIRSCH.
- PETERS, J. P. and VAN SLYKE, D. D.: Quantitative Clinical Chemistry. The Williams and Wilkins Co. Baltimore. 1937. Volume 1:1028, 1033.
- PETERS, J. P., WAKEMAN, A. M., EISENMAN, A. J. and LEE, C.: The Acidosis of Nephritis. — *J. Clin. Invest.* 1929:6:517.
- PETRUNKIN, M.: Über die Veränderungen im Gange der Blutzuckerkurven während einiger infektiöser Krankheiten. — *Z. Kinderhk.* 1935:57:138.
- PETSCHACHER, L.: Die Serumeiweisskörper bei Tuberkulose und deren Beziehungen zur Viskosität des Blutserums und zur Blutkörperchensenkungsgeschwindigkeit. — *Z. exper. Med.* 1923:36:22.
- PITKÄNEN, H.: Über den Vitaminhaushalt in der Schwangerschaft und im Wochenbett bezüglich der A- und B₁-Vitamine, der Nikotinsäure und des C-vitamins. — *Diss. Helsinki.* 1944.
- RABINOWITCH, I. M.: Influence of Infection upon Reaction of Diabetic to Insulin Treatment; Report of Unusual Case. — *Canad. Med. Assn. Jour.* 1932:26:551. Quoted by MARBLE.
- RANSTRÖM, S.: On the Terms »Essential Hyperglobulinemia» and »Premyeloma». — *Acta Med. Scand.* 1946:124:134.
- RAUNIO, O.: Untersuchungen über den C-Vitamingehalt der Nahrung in den finnischen Tuberkulosesanatorien. — *Diss. Acta Soc. Medic. Fenn. Duodecim. Ser. A. Tom. XXIII. Fasc. 2.* 1941.
- RATZAN, M. G. and THOMPSON, S. A.: Hypoproteinemia in Surgery of the Thorax. — *Amer. J. Surg.* 1945:70:213.
- REDTENBACHER, W.: Quoted by LAUTROP and MADSEN.
- REIMANN, H. A.: Recovery from Amyloidosis. — *J. Amer. Med. Assoc.* 1935:104:1070.
- RINEHART, J. F., GREENBERG, L. D. and CHRISTIE, A. A.: Reduced Ascorbic Content of Blood Plasma in Rheumatic Fever. — *Proc. Soc. Exper. Biol. a. Med.* 1936:35:350.
- RISKA, N.: NaCl-utsöndringen i urinen vid pleuriter. — *Nord. Med.* 1945:27:1897.
- ROHDENBURG, G. L. and POHLMAN, H. F.: Hyperglycemia in its Relation to Immunity. — *Am. J. Med. Sci.* 1920:159:853.
- RONZONI, E., KOECHIG, L. and EATON, E. P.: Rôle of Lactic Acid in the Acidosis of Ether Anesthesia. — *J. Biol. Chem.* 1924:61:465.
- ROOT, H. F.: The Association of Diabetes and Tuberculosis. — *New Engl J. Med.* 1934:210:127.
- ROSCHER, F.: Investigations of Postoperative Acidosis and Ketonuria. — *Acta Chir. Scand.* 1933. Suppl. 29.

- ROSENBLATT, M. B.: Recovery from Generalized Amyloidosis Secondary to Pulmonary Tuberculosis; Report of Case. — *Arch. Int. Med.* 1936:57:562.
- SALKOWSKI, E.: Untersuchungen über die Ausscheidung der Alkalisalze. — *Virchows Arch.* 1871:53:209.
- SALVESEN, H. A.: Plasma Proteins in Normal Individuals. — *Acta Med. Scand.* 1926:65:147.
- SANDELOWSKY, J.: Blutkonzentration bei Pneumonie. — *Dtsch. Arch. klin. Med.* 1909:96:445.
- SASKIN, S. and MIRSKY, A.: The Influence of Progressive Toxemic Liver Damage upon the Dextrose Tolerance Curve. — *Amer. J. Physiol.* 1935:112:649.
- SCHADE, H., NEUKIRCH, P. und HALPERT, A.: Über lokale Acidosen des Gewebes und die Methodik ihrer intravitalen Messung, zugleich ein Beitrag zur Lehre der Entzündung. — *Z. exper. Med.* 1921:24:11.
- SCHALLOCK, G.: Über Organveränderungen beim infizierten Schussbruch. — *Dtsch. Mil.arzt.* 1943:8:515.
- SCHPILEWSKY, E.: Experimentelle Beiträge zur Frage der amyloiden Degeneration. — *Zbl. Bakter. etc.* 1899:25:849.
- SCHOCH, A.: Über Eiweisschwankungen im Blutserum bei akuten Infektionskrankheiten. — *Schweiz. med. Wschr.* 1926:42:1017.
- SCHOEN, R.: Zur Kenntnis der Morphinwirkung beim Menschen. — *Arch. Exper. Path.* 1923:101:365.
- SCHROEDER, H.: Die Ausscheidung der Ascorbinsäure im gesunden und kranken Organismus. — *Klin. Wschr.* 1935:14:484.
- SCHÖNBERGER, E. und ROSENBLATT, J.: Über intravenöse Kongorotinjektionen nach Bennhold. — *Wien klin. Wschr.* 1925:38:1113.
- SEITZ, E.: Das Verhalten des Blutzuckers bei chirurgischen Erkrankungen. — *Mitt. Grenzgeb. Med. u. Chir.* 1922:34:514.
- SICK, W.: Blutzuckerkurven bei akuten fiberhaften Infekten. — *Münch. med. Wschr.* 1931:15:609.
- SIEDEK, H. and ZUCKERKANDL, F.: Untersuchungen über Na- und Cl-Stoffwechsel. — *Wien. klin. Wschr.* 1935:85:1029.
- SIDELIN, G.: Hypochloreaemia in Pulmonary Tuberculosis. — *Acta Tub. Scand.* 1934:8:265.
- SIRALA, M.: Lisiä tietoihimme ihmisveren keittosuolapitoisuudesta. — *Duodecim.* 1917:33:155.
- SIMOLA, P. E.: Miltä näyttää Suomen nykyinen ravintotilanne. — *Duodecim.* 1941:57:132.
- SIMOLA, P. E. and BRUNIS, E.: Vitamine und Immunität. Über Komplementgehalt und Immunhämolysinbildung bei A- und C-Avitaminose. — *Biochem. Z.* 1933:258:228.
- SJÖVALL, H.: Experimentelle Untersuchungen über das Blut und Blutbildenden Organe — besonders das lymphatische Gewebe — des Kaninchens bei wiederholten Aderlässen. — *Diss. Lund.* 1936.

- SOISALO, P.: Über die Blutzuckerkurve des gesunden Menschen. — Diss. Acta Soc. Medic. Fenn. Duodecim. Ser. B. Tom. XIII, Fasc. 2. 1930.
- SPERRY, W. M.: The Concentration of Total Cholesterol in the Blood Serum. — J. Biol. Chem. 1937:117:391.
- STADIE, W. C., AUSTIN, J. H. and HOWARD, W. R.: The Effect of Temperature on the Acid-Base-Protein Equilibrium and its Influence on the CO₂ Absorption Curve of Whole Blood, True and Separated Serum. — J. Biol. Chem. 1926:66:901.
- STADIE, W. C. and MARTIN, K. A.: The Thermodynamic Relations of the Oxygen- and Base-Combining Properties of Blood. — J. Biol. Chem. 1924:60:191.
- STEINER, A. and DOMANSKI, B. A.: Serum Cholesterol and Atherosclerosis in Chronic Glomerulonephritis. — Amer. J. Med. Sci. 1942:204:79.
- STRÖMBECK, J. P.: Diabetes och Kirurgi. — Forhandlingar ved Nordisk Kirurgisk Forenings 22 Møde i Oslo 1939.
- SUNDERMAN, F. W.: Studies of Serum Electrolytes. — J. Clin. Invest. 1929:7:313.
- SUNDERMAN, F. W., AUSTIN, J. H. and CAMAC, J. G.: Studies in Serum Electrolytes. — J. Clin. Invest. 1926:3:37; 1928:6:37.
- SWEANY, H. C.: The Alkali Reserve in Tuberculosis. — Amer. Rev. Tbc. 1923:7:193.
- SWEENEY, J. S.: Effect of Toxemia on Tolerance for Dextrose and on the Action of Insulin. — Arch. Int. Med. 1928:41:420.
- TARAN, B. A. and ECKSTEIN, A.: The Standardization of the Congo Red Test for Amyloidosis. — Amer. J. Med. Sci. 1942:203:246.
- THOMPSON, W. D., RAVDIN, I. S. and FRANK, O. L.: Effect of Hypoproteinemia on Wound Disruption. — Arch. Surg. 1938:36:500.
- THORESEN, E.: Forandringer i blodsukkerspeilet under og efter operative inngrep i eternarkose. — Norsk. Mag. Lægevidensk. 1932:499.
- THORNTON, T. F., ADAMS, W. E. and SCHAEFER, P. W.: Hypoproteinemia in Thoracic Surgery. — Surg. etc. 1944:79:368.
- TRÜCK: Ref. CONRAD.
- TIITINEN, E.: Veriteitse synttyvästä luumädästä. — Diss. Duodecim. 1944. Suppl. 4.
- TIITINEN, E.: Über die Veränderungen des Sternalpunktates und des Blutbildes bei der akuten und chronischen hämatogenen Osteomyelitis. — Acta Med. Scand. 1944:119:VI.
- TRIER, E. and PEDERSEN, H.: On the Chemical and Clinical Recognition of Hypovitaminosis C. — Acta Med. Scand. 1941. Suppl. 123:418.
- TÖNNIS, W.: Experimentelle Untersuchungen zur Entstehung der postoperativen Blutveränderungen. — Beitr. klin. Chir. 1929:147:249.
- UNDERHILL, F.: Studies in Carbohydrate Metabolism. — J. Biol. Chem. 1916:25:463.
- VAHLQUIST, Bo C:SON: Das Serumeisen. — Diss. Uppsala. 1941.

- VAN SLYKE, D. D.: Note on a Portable Form of the Manometric Gas Apparatus, and on Certain Points in the Technique of its Use. — *J. Biol. Chem.* 1927:73:121.
- VAN SLYKE, D. D. und NEILL, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement. — *J. Biol. Chem.* 1924:61:523.
- VAN SLYKE, D. D., STILLMAN, E. and CULLEN, G. E.: Alveolar, Carbon Dioxide and Plasma Bicarbonate in Normal Men during Digestive Rest Activity. — *J. Biol. Chem.* 1917:30:401.
- VARA, P. and TIITINEN, E.: Clinical Investigations on the O₂ and CO₂ Content and the Alkali Reserve of Arterial and Venous Blood Specifically in Connection with Operations. — *Acta Obstetr. Scand.* 1947:27:176.
- VARCO, R. L.: Preoperative Dietary Management for Surgical Patients. — *Surgery.* 1946:19:303.
- VESA, A. and KALAJA, T.: Beiträge zur Kenntnis des Cholesterin- und Phosphatidstoffwechsels bei Diabetes, Nieren- und Leberkrankheiten. — *Acta Soc. Medic. Fenn. Duodecim. Ser. A. Tom. XXI. Fasc. 2.* 1939.
- WACHSMUTH, W.: Die Kriegs-Wundkachexie. — *Dtsch. Mil. arzt.* 1943:8:495.
- WACHSMUTH, W. and HEINRICH, G.: Hypovitaminose und Osteomyelitis. — *Klin. Wschr.* 1938:17:269.
- WALDENSTRÖM, H.: On the Formation and Disappearance of Amyloid in Man. — *Acta Chir. Scand.* 1928:63:479.
- WEGEMER, E. and BÜSING, K. H.: Die Blutbactericide und der Blut-ascorbinsäurespiegel im jahreszeitlichen Verlauf bei gesunden und Tuberkulosekranken. — *Beitr. Klin. Tbk.* 1942:98:666.
- WESTERGAARD, F.: Om Blodets Indhold af Vitamin C. — *Hosp. tid.* 1937:80:713.
- WHIPPLE, G.: Protein Production and Exchange in the Body, including Hemoglobin, Plasma Protein and Cell Protein. — *Amer. J. Med. Sci.* 1938:196:609.
- WHITBECK, B. H.: Liver Meal in the Treatment of Amyloidosis in Surgical tuberculosis. — *J. Bone Surg.* 1932:14:85.
- WHITEHORN, J. C.: Simplified Method for the Determination of Chlorides in Blood or Plasma. — *J. Biol. Chem.* 1921:45:449.
- WHITNEY, J. L.: Studies on Acidosis. The Immediate Cause of Death, and Remarks on the Acidosis of Nephritis. — *Arch. Int. Med.* 1917:20:931.
- WIDAL: Quoted by JOHANSSON (1945).
- WIDENBAUER, F.: Der Vitamin C-Haushalt des Menschen unter verschiedenen Verhältnissen. — *Klin. Wschr.* 1937:16:600.
- WILDER, T. S. and DRAKE, T. G. H.: Metabolism of Chloride and Total Fixed Base in Pneumonia and the Relation to Salt and Water Retention. — *J. Clin. Invest.* 1929:7:353.

- WILLIAMS, J. L. and DICK, G. F.: Decreased Dextrose Tolerance in Acute Infectious Diseases. — *Arch. Int. Med.* 1932:50:801.
- WINDFELD, P.: Beiträge zur Kenntnis der postoperativen Blutveränderungen. — *Acta Chir. Scand.* 1933. Suppl. 22.
- WOLBACH, S. B.: Controlled Formation of Collagen and Reticulum. A Study of the Source of Intercellular Substance in Recovery from Experimental Scorbutus. — *Amer. J. Path.* 1933:9:689.
- WOLF, J. E.: Untersuchungen über den Vitamin C-Gehalt des Blutes bei Lungentuberkulösen. — *Schweiz. med. Wschr.* 1945:75:506.
- WORTIS, H., LEIBMANN, J. and WORTIS, E.: Vitamin C in the Blood. — *J. Amer. Med. Assoc.* 1938:110:1896.
- WUNDERLY, C. H.: Chemie der Plasmaproteine. — WUHRMANN, F. und WUNDERLY, C. H.: Die Bluteiweisskörper des Menschen. Benno Schwabe and Co. Basel. 1947.
- ZERBINI, E. J.: The Importance of Ascorbic Acid (Vitamin C) in Chest Surgery. — *J. Thorac. Surg.* 1945:14:309.

